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Mapping the future of common diseases: lessons from psoriasis

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1. ABSTRACT

Psoriasis (OMIM*177900) is a common, chronic, hyperproliferative inflammatory disorder of the skin affecting approximately 2% of Caucasians. Despite the prevalence of psoriasis in general population, significant differences in the incidence among Japanese, Eskimos, West Africans, north American blacks and American natives are well known. The cause for these variations are likely to be both genetic and environmental. Independent genomewide scans have suggested the involvement of a large number of chromosomal regions (loci), but so far only poor susceptibility genes have been suggested. We discuss genetic basis of the disease, results and interpretations of relevant studies, with particular regard to study design and future perspectives. Indeed to date, mapping genes which contribute to complex diseases is one of the major challenge in the post-genomic era.

"But remember throughout that no cause is efficient without a predisposition of the body itself, otherwise, external factors which affect one would affect all." (Galen, 130-200 CE)

2. INTRODUCTION

Psoriasis (OMIM*177900) is a common, chronic and papulosquamous inflammatory skin disease affecting approximately 2% of the population in Western countries. Because of its chronicity, unpredictability, and the associated severe symptoms, psoriasis is often very disruptive to patients' lives, contributing physical and psychological burdens. The most common form of psoriasis (psoriasis vulgaris or plaque-type psoriasis) is characterized by chronic scaling papules and plaques in characteristic sites of the body, largely related to repeated minor trauma: scalp, elbows, forearms lumbosacral region, knees, hands, and feet. There are many clinical variants of psoriasis distinguished by appearance and distribution of lesions. Some of these distinctions may be indicative of the underlying heterogeneity of the disorder. Although rarely fatal, psoriasis is a lifelong condition which affect greatly the quality of life of patients. Population surveys, showed that males and females are equally affected but reported disparate incidence rates of psoriasis among different geographic regions. In particular, this disorder is rare among Japanese, Eskimos, West Africans and North

American blacks; and very uncommon in North American and South American natives. These variations result from complex, aberrant relationship between the skin and immune system, as well as genetic makeup and environmental factors.

The clinical picture of psoriasis is accompanied by the occurrence of psoriatic arthritis (PsA), a seronegative form of arthritis which has been recognized since the late 19th century (1,2,3). Recently, the frequency of joints involvement in psoriasis patients was observed to be more common than suspected (4). In particular many reports have showed that psoriatic arthritis affects as much as 10% of patients with psoriasis (5); about 95% of patients with psoriatic arthritis have swelling in joints outside the spine, and more than 80% of people with psoriatic arthritis have nail lesions (6). It should be outlined that the evidence of an imprinting effect reported for PsA which appears to be twice as common in females (7).

Although psoriasis affects people of all ages, a strong tendency for disease onset in early adulthood has been described for patients who develop psoriasis due to genetic transmission. In this regard, two main peaks of age of onset have been described: the largest is between 20 and 30 years, and a smaller peak occurs at 50-60 years, leading to the hypothesis of the existence of two distinct forms of disease analogous to diabetes mellitus (8). This report analyses the state of the art of genetic studies of psoriasis particularly addressed to determine the existence of a correlation between genotype and phenotype: in other words the link between genetics, clinics and therapeutic challenges.

2.1. Genetic epidemiology

Twin studies provided important information concerning the roles of genetics and environmental risk factors on disease risk. In addition population-based studies addressed to asses the existence of family-clustering of disease providing evidence that genetic factors may be operating. Family-based studies performed on psoriasis indicated that psoriasis is a heritable disease with a polygenic mode of inheritance with variable penetrance (9). But how much does is the relative contribution of genes with respect to the environmental factors in psoriasis pathogenesis?

On the basis of the available population epidemiological studies the recurrence risk of psoriasis in first-degree relatives of affected subjects is about 10 times greater than that seen in general population (10;11). In addition, twin studies calculated the hereditability of psoriasis: as expected, the concordance rate of psoriasis in monozygotic twins was significantly higher (65-72%) compared to concordance rate observed in dizygotic twins (15-30%). It is to notice that when monozygotic twins are concordant for the disease, these tends to be similar in age of onset, lesion's localization, severity. This trend was not observed in dizygotic twins, suggesting that genetic factors strongly influence many clinical parameters. The hereditability however, does not provide information concerning the mode of inheritance, the number of loci, or the magnitude of individual locus effects on the disease. Furthermore, the inference should be restricted to the population and the environment in which the trait is measured. Thus, hereditability is a function of the disease measured at a point in time on a population in a specific environment. Changing any of these parameters may results in a different hereditability, as demonstrated by the fact that the observed rate of concordance is quite dissimilar between the different populations (7). These data confirm that psoriasis is due to a combination of genetic predisposition and environmental assaults. It is now universally acknowledged that the nature of genetic predisposition such as the relative contribution (penetrance) of single alleles may be dissimilar in different populations. In this regard a wide range of environmental agents can cause psoriasis flares (12). These include HIV infection (13), streptococcal infections, contact dermatitis, interferons (IFNs)-α-β and γ, interleukin-2 (IL-2), granulocyte colony-stimulating factors (G-CSF), lithium, abrupt cessation of systemic corticosteroids, α-blockers, angiotensin-converting enzyme inhibitors and antimalarials (14-15). In particular, streptococcal infection of the upper respiratory tracts plays a major role in the development of psoriasis and its exacerbation and seem to induce the form guttate of psoriasis (16, 17, 18). We have to consider that even traumas can cause the development of a psoriatic lesion, a feature known as "Koebner phenomenon". This phenomenon was described for the first time by Heinrich Koebner in 1872 and refers to the appearance of isomorphic pathological lesions in the uninvolved skin of psoriatic patients as a consequence of injury or stress to the epidermis. The Koebner phenomenon, although particularly frequent in psoriasis patients, is not limited to psoriasis but it has been described for a wide range of diseases.

2.1.1. Clinical data

As described, the clinical feature of psoriasis is a papulosquamous disease with variable morphology, distribution, severity, and course. Papulosquamous diseases are characterised by scaling papules (raised lesions <1 cm in diameter) and plaques (raised lesions >1 cm in diameter). Despite the classic presentation described above, psoriasis can be highly variable in morphology, distribution, and severity. In particular, the morphology can range from small tear shaped papules (guttate psoriasis) to pustules (pustular psoriasis) and generalised erythema and scale (erythrodermic psoriasis). In addition, these different forms of psoriasis may be localised or widespread and disabling. Further, psoriasis may have a variable course presenting as chronic, stable plaques or may present acutely, with a rapid progression and widespread involvement (19).

2.1.2. Pathogenesis

The pathogenesis of psoriasis remains unclear, and it is controversial as to whether psoriasis results from a primary abnormality in epidermal keratinocytes or from deregulation of the immune system, although these pathogenetic pathways are not mutually exclusive. The aberrant function of T lymphocytes and dendritic cells has been proposed to be important in the maintenance of psoriasis, but it is not *conditio sine qua non* for the disease.

The above reported clinical features of psoriasis can be better explained by impressive growth and dilation of superficial blood vessels (redness) and remarkable hyperplasia of the epidermis. In psoriatic epidermis, keratinocytes proliferate and mature rapidly so that terminal differentiation, normally occurring in granular keratinocytes and then squamous corneocytes, is incomplete. Alterations of the keratinocytic cell cycle, which shortens from 311 to 36 hours, accounting for a 28 fold increase in epidermal cell production: in other words, the physiological process of re-epithelization observed during wound healing, in psoriasis is constitutive and represents an abnormal exaggerated wound-healing response (20).

In these perspectives, we can summarize that after a stimulus, dendritic cells and T cells become activated and determinate the activation of nuclear factor-kB (NF-kB) and the release of cytokines, such as tumor-necrosis factor-α, chemokines, proteases and many other inflammatory mediators, which induce a wound-healing-like phenotype in the epidermis that is characterized by keratinocyte proliferation. At this point the specific interaction between T cells and endothelial cells or/and basement membrane constituents determinates an additional and massive migration of T cells into epidermis. In this perspective, the chronic psoriatic plaque is characterized and maintained by an autocatalytical cycle of continuous reciprocal activation of T cells and dendritic-cells (15).

2.1.3. Genetics

It is now universally accepted that psoriasis has both genetic and environmental aetiologies. As reported before, now we know many environmental factors which can trigger psoriasis. But what do we know about genetic component of psoriasis? Here below is reported the current knowledge about mode of inheritance, penetrance, susceptibility loci and putative associated genes.

2.1.4. Mode of inheritance and penetrance

There is a significant level of uncertainty concerning the mode of inheritance of psoriasis. Actually, the more appropriate description of psoriasis genetics is that psoriasis is a heritable disease with a polygenic mode of inheritance with variable penetrance (9). One of the first studies (21), performed in a single large family through many generations supported a dominant inheritance. On the other hand, more recent papers, performed on a large collection of psoriatic Swedish families, showed dissimilar data. In particular, on the basis of the risk to the child of an unaffected couple randomly selected from the general population, segregation data reported were compatible with an autosomal recessive inheritance of psoriasis (22-23).

Concerning the penetrance of disease, of course it depends on the specific susceptibility genotype considered and it is very difficult to assess definitely. The above mentioned study (21) reported that the penetrance of disease in a very large family tree was reduced to about 60%. Obviously, for genetic counselling it is easier for the clinicians to accept and use data on the empiric risk of the children getting psoriasis rather than using a genetic model that includes mode of inheritance, gene frequency, heterogeneity and penetrance of the genotype.

3. LINKAGE STUDIES IN PSORIASIS

It is well known that psoriasis can be arise from complex interactions between environmental triggers and several distinct susceptibility genes (genotypes) according with a high degree of genetic heterogeneity (24). These data have been supported by different linkage studies performed in psoriasis. In the past 10 years, a lot of genomewide linkage scans have been conducted in psoriatic families. These works have suggested the involvement of at least 20 potentially susceptibility chromosomal regions (Figure 1) (25) but positive data were replicated only in few cases (26): the only locus consistently and independently identified is that harbouring the associated HLA class I region (PSORS1). This is because: (i) the frequency of psoriasis is so high that sometimes sporadic cases may be mistaken for familial segregations; (ii) the existence of genetic heterogeneity decreases the ability to detect linkage by combining scores from different families; (iii) the evidence of linkage to other regions is weaker, presumably because the penetrance of these alleles is lower than that observed for PSORS1; (iiii) some susceptibility loci may be found only in specific populations. The importance and the significance of these loci will be here discussed.

3.1. PSORS1

It has been nearly 30 years since researchers first recognized that certain variations in the HLA system (MHC class I and II) on chromosome 6p conferred an increased risk. In particular, many independent genomewide scans have mapped PSORS1 on chromosome 6p21.3. This region contains the major histocompatibility complex (MHC), in which are mapped the genes for human leucocyte antigens (*HLA*). This locus is considered the major susceptibility locus for psoriasis, which accounts for about 30% to 50% of the genetic contribution to the disease (27-28-29). Many works have associated psoriasis with HLA-Cw*06, but the identity of the HLA class I causative allele is currently controversial. Using serological markers, it has been demonstrated that type 1 psoriasis with age at onset <30 was associated with the *HLA-Cw6* while type 2 psoriasis, showing an age of onset >30 was associated with *HLA-Cw2* and *HLA-B27*; afterwards, it's been reported association with class I antigens (*HLA-B13* and *HLA-B57*) and with class II antigens (*HLA-DR4* and *HLA-DR7*) (8; 9). Further haplotype studies have confirmed association of *Cw6* and *B57* (30).

The existence of a conservative linkage disequilibrium block in the susceptibility region and the high degree of genetic heterogeneity of psoriasis have led to a controversial mapping of PSORS1. Independent efforts were conducted to discriminate the markers from the true susceptibility allele (31;32;33), but there was no agreement about a common overlapping susceptibility region. To resolve this matter an additional dense map of SNPs (Single Nucleotide Polymorphisms) was typed in 171 nuclear families, revealing a 10 Kb core risk haplotype,

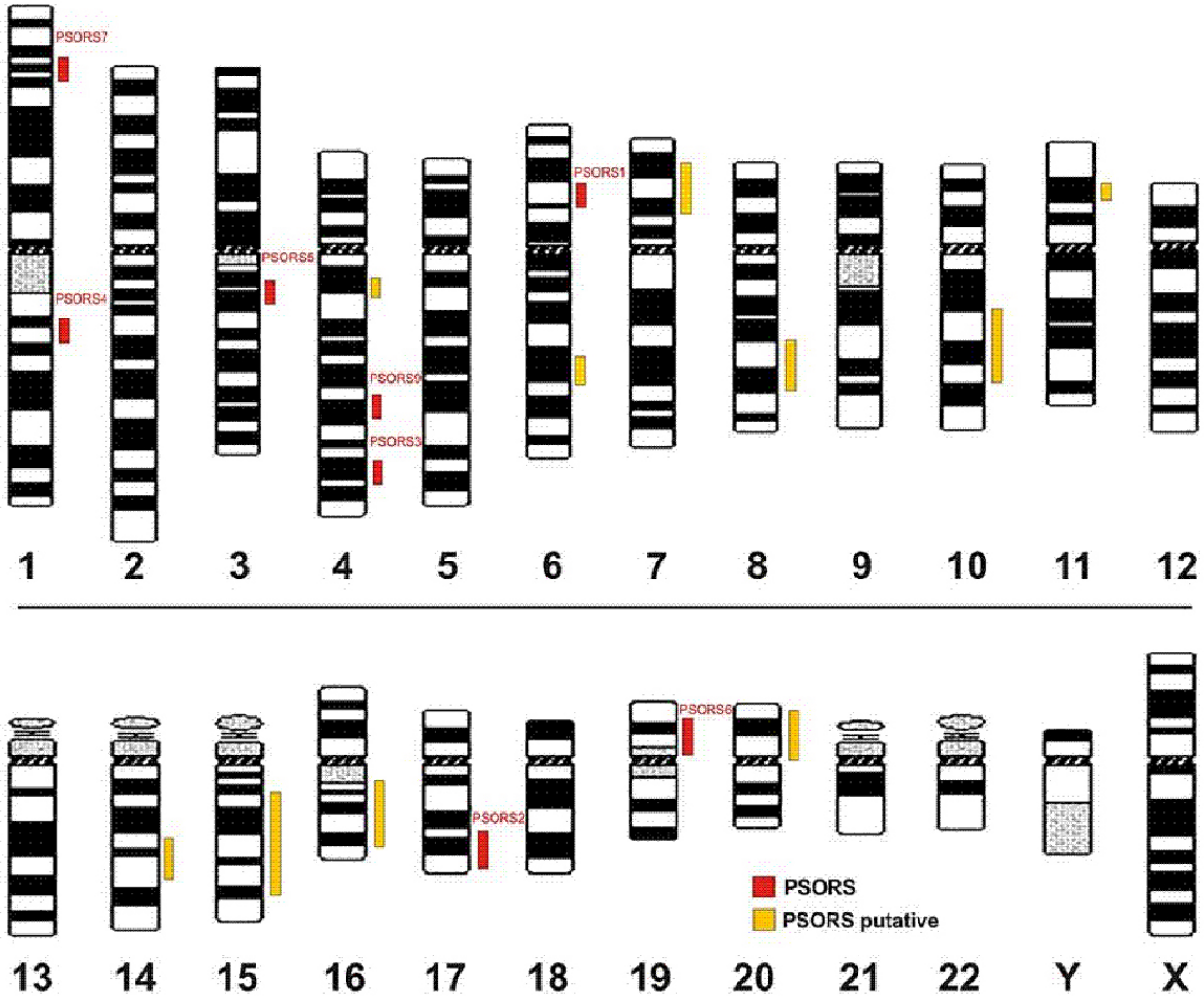

Figure 1. Localization of human psoriasis susceptibility loci.

surrounding *HLA-C* gene (34). Within the identified susceptibility region reside at least 3 genes carrying disease associated alleles: *HLA-C*, α-Helix Coiled coil Rod homologue (*HCR*) and Corneodesmosin (*CDSN*). However, the existence of a rare susceptibility haplotype (cluster D), originating from a double recombination event could exclude *HCR* gene as candidate, suggesting that alleles of *CDSN* and *HLA-C* genes might be required to confer psoriasis susceptibility (34). Finally, a recent study on the Sardinian population typed 17 polymorphic markers in a 525-kb interval around the HLA-C locus and confirmed a marked association of *CDSN*TTC* allele (35). It should be outlined that in the Sardinian population the association of *CDSN*TTC* allele is not influenced by the presence of specific *HLA-C* alleles. In particular, they revealed a psoriasis-susceptibility haplotype (PSH) carrying 5 loci with alleles strongly associated with psoriasis. Further analysis of extended haplotypes showed that the PSH was not only present in the traditional psoriasis-susceptibility extended haplotypes but also on a haplotype of Sardinian origin found to be associated with psoriasis because of an ancestral recombination with one of the susceptibility haplotypes carrying a particular *HLA-C* allele. To summarize, the presence of an ancestral recombination between HLA-Cw*06 and *CDSN* reported in the Sardinian population demonstrate the independence of the association with the *CDSN*TTC* allele but cannot exclude the existence of minor specific interaction between associated allele with the rest of the PSORS1. Evidence supporting corneodesmosin as the main candidate gene of PSORS1 locus arose from functional experiments (36) demonstrating that mRNAs transcribed from the specific *CDSN* risk haplotype present a 2-fold increase in stability, compared with those transcribed from a neutral haplotype. In particular, the presence of T allele of a single synonymous SNP (*CDSN*971T*) accounts for the increased stability of *CDSN* transcript observed in psoriatic cells. Despite the large efforts of several research groups, to date we can't define definitely the identity of PSORS1 gene/s.

3.1.1. PSORS2

The first evidence of the existence of a non-MHC susceptibility locus to psoriasis was obtained for the chromosome 17q25 (37). In this study a genomewide scan,

using polymorphic microsatellite markers was performed in eight multi-generational families of USA origin. In particular, the greatest evidence for linkage was obtained in a large family (more than 20 affected) in which the penetrance of the disease was very high (80-90%) resulting in a LOD score of 5.33. Strong evidence for genetic heterogeneity was suggested, establishing that half the families were unlinked to 17q25 locus, designated as PSORS2 by OMIM database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). Further linkage studies confirmed these results in three independent populations, such as Germany, Ireland and Sweden (38; 39; 40). A finer localization of PSORS2 on chromosome 17q23-25 revealed an association peak very close to a new cluster of genes, coding for an immunoglobulin superfamily (41). This region spanned about 250 Kb and includes al least seven genes (*CMRF35H*, *CMRF-35A*, and five *CMRF35A*-like genes). When 76 additional inner markers were used (42), two distinct peaks of significant association, separated by 6 Mb, were uncovered. The proximal peak lies 80 kb distal to D17S1301 and contains two genes: *SLC9A3R1* (solute carrier family 9, isoform 3 regulatory factor 1) and *NAT9* (unknown gene). The distal peak of association is in *RAPTOR* (p150 target of rapamycin (TOR)-scaffold protein containing WD-repeats). In the proximal peak, a disease-associated allele (A) of marker 9, mapped between *SLC9A3R1* and *NAT9* removes a binding site for the runt-related transcription factor RUNX1. The demonstrated specific binding to the wild-type (G allele of marker 9) RUNX1 binding site, led to an intriguing functional explanation of genetic predisposition, since an allele removing a binding site for RUNX1 has previously been associated with another inflammatory, autoimmune disease: systemic lupus erythematouos (OMIM #152700). Typing of additional 233 parent-offspring trios with psoriasis for 8 representative SNPs (single nucleotide polymorphisms) selected from both of the association peaks previously identified led to a replication of these data in an independent population (43). However, recently an independent study confirmed the evidence of linkage but failed to support association (44). In particular, 1,285 affected individuals selected from 579 pedigrees were genotyped for three SNPs surrounding the RUNX1 binding site and for three SNPs in the third intron of the *RAPTOR* gene. In addition, 274 of these pedigrees were also genotyped for 32 microsatellite markers spanning chromosome 17. Although evidence for a linkage mapped 1.7 cM distal to the RUNX1 binding site was revealed, they failed to detect any evidence for association to individual SNPs or haplotypes in either of the previously-identified peaks of association. An additional study, performed on our large cohort of Italian psoriatic arthritis patients failed to reveal evidence of association to individual SNPs or haplotypes selected from both of the association peaks previously identified (E.G. unpublished data).

Recently, an additional genomewide scan (45) performed in a 5-generation family with psoriasis revealed a value of very significant linkage (LOD=7.164 (theta = 0.01)) for the marker D17S928. The following pedigree disequilibrium test performed by typing additional 202 SNPs refined and confirmed the linkage locus in a region within 400 kb of the 17q terminus. It should be outlined that these data supported the existence of an additional susceptibility locus of psoriasis on chromosome 17.

3.1.2. PSORS3

Linkage analysis of five extended families from Northern England and Ireland generated a LOD score of 3.03 for marker D4S1535 on q-terminal part of chromosome 4, under a dominant model with 70% penetrance (38). Other linkage scans have identified a more proximal region of chromosome 4q (46-47). Although recently no evidence for linkage on chromosome 4 was detected by International Psoriasis Genetic study (26), it should be outlined that a meta-analysis study conducted on an extended number of families (48) originating from northern Europe revealed a strong evidence of linkage for markers mapping on chromosome 4q. Associated markers defined a new susceptibility region on chromosome 4q28-31. To date, these findings do not permit us to conclude if chromosome 4q harbours distinct susceptibility loci or if the exact position of susceptibility region has to be better defined by additional genotyping in independent populations.

3.1.3. PSORS4

The existence of a susceptibility locus on chromosome 1cen-q21 (PSORS4) was first proposed by our group (49) through a genomewide scan on 22 families originating in continental Italy (LOD=3.75). Later, evidence of epistasis between PSORS1 locus and PSORS4 locus confirmed the polygenic nature of psoriasis and therefore the fact that the disease requires the presence of additional susceptibility alleles (50). It should be stressed that PSORS4 maps within the epidermal differentiation complex (EDC) a cluster of related genes active on epithelial differentiation. Expression analysis of many EDC genes revealed an up-regulation of *S100A8*, *S100A9*, and *S100A7*, only in those families previously demonstrated to be 1q21 linked. Intriguingly, the up-regulation of *S100A8* e *S100A9* was also observed in the hyper-thickened epidermis of human wounds, suggesting a potential role of these genes in influencing the balance between keratinocyte proliferation and differentiation (51). By using a linkage disequilibrium approach, the PSORS4 region was refined within a region of about 100 kb mapped between two markers: D1S2346 and 140J1D (52). These results, replicated in an independent dataset of patients, revealed the existence of a single positional candidate gene *LOR*, encoding for loricrin, the major component of cornified envelope in human skin. By performing genotyping, haplotyping and expression analysis of the gene we failed to detect evidence for genetic association in a large cohort of Italian nuclear families (53). Since the psoriasis susceptibility loci on chromosome 1q21 (PSORS4-ATOD2), 17q25 (PSORS2-ATOD4) and 20p (-ATOD3) are closely coincident with region linked to atopic dermatitis (54) we performed a combined linkage disequilibrium approach in both distinct datasets of psoriasis and atopic dermatitis patients. In this study, we performed an association fine-mapping to refine PSORS4 and ATOD2 loci in order to verify the existing overlap

between these loci on chromosome 1q21 (55). Genotype and haplotype analysis of PSORS4 and ATOD2 led us to detect high significant *p*-value for psoriasis (p= 0.000008) and atopic dermatitis (p=0.0046) evidencing a marked co-localization limited to an interval of 42 Kb (Giardina et al., submitted). This interval identifies a small region containing only *LOR*. Although classical genetics analysis did not reveal evidence of association in both diseases, expression profiles of *LOR* gene in cultured keratinocytes demonstrated an up-regulation of *LOR* in atopic dermatitis and a down-regulation in psoriasis. On these bases, the genetic susceptibility to psoriasis and atopic dermatitis on chromosome 1q21 could be explained by a disease-specific differential expression of loricrin (56). These findings support the hypothesis of a functional role of *LOR* gene which may be genetically explained by SNP/SNPs mapped in a LCR (locus control region) distal to the coding region analysed.

3.1.4. PSORS5

Linkage to chromosome 3q21 has been shown to psoriasis in Swedish population (57). A further refinement of PSORS5 locus was obtained by analysis of additional 195 psoriatic Swedish families (58). In particular, a transmission disequilibrium test performed in 47 multiaffected families and 148 nuclear families lead to the identification of association (p-value of 3.8×10^{-5}) with a five markers haplotype spanning the 3' half of solute carrier family 12, member 8 (*SLC12A8A*). The predicted protein shares 30-40% homology with the family of cation/chloride cotransporters and it should be outlined that many members of solute carrier genes have been associated with inflammatory disease. In particular, *SLC22A5* was reported associated with Crohn disease (59) and SLC22A4 was reported associated in both Crohn disease (59) and rheumatoid arthritis (60-61). Moreover, the gene *SLC9A3R1* above mentioned, mapped on chromosome 17q25 is associated with psoriasis (42). These findings confirm that many of the so far identified disease-associated genes seem to be linked to multiple disorder. At this regard, functional studies on these proteins may be decisive to uncover common pathogenetic pathways depending by genetic variants in cation-transporter genes in a wide range of inflammatory diseases.

3.1.5. PSORS6

Linkage to chromosome 19p13 was reported in an extended genomewide scan perfomed in 32 large families (162 affected and 195 unaffected individuals) (62). The following linkage disequilibrium approach was conducted to refine the susceptibility interval. In particular, a new recruited sample of 210 nuclear families was typed by using a densely-spaced microsatellite markers map (63) leading to a replication of association findings.

3.1.6. PSORS7

A putative additional susceptibility locus to psoriasis was mapped on chromosome 1p in British Caucasian population (64). A genomewide linkage analysis in 158 families revealed linkage at 6p21 and at 1p. Although no replication of these data have been reported, it should be outlined that susceptibility interval harbours *PTPN22* gene, demonstrated associated with a wide range of autoimmune diseases such as rheumatoid arthritis (65), type I diabetes (66-67), systemic lupus erythematosus (SLE) (68), Graves' disease (69).

3.1.7. Chromosome 16

A genomewide scan by genotyping 224 sib-pairs originating from United States and Germany supported the existence of a susceptibility locus to psoriasis on chromosome 16q (39). A subsequent work of psoriasis consortium confirmed the evidence of linkage on this chromosome, such as a study on psoriatic arthritis in a large cohort of Icelandic families (26-70). Within this locus, overlapping with Crohn's disease susceptibility region, the gene *CARD15*/*NOD2* has been convincingly shown to confer susceptibility to Crohn's disease (71;72). Successively, a study conducted on an isolated population (Newfoundland) supported the association of *CARD15* variants in psoriatic arthritis patients (73). However, association studies, have ruled out the involvement of *CARD15* as candidate gene for both psoriasis (74;75) and psoriatic arthritis (76). These findings suggest that *CARD15* itself could be a genetic marker of the true susceptibility locus and that the positive association found in isolated population may be the result of a linkage disequilibrium due to a founder effect.

4. CONCLUSIONS AND PERSPECTIVES

Despite extensive research efforts in both the academic and commercial sectors, the success rate of linkage analysis has been considerably lower than expected. Indeed, identifying genes that contribute to complex diseases is a major challenge in the post-genomic era. Although there is strong evidence for a genetic component of common diseases, currently little is known about the specific genetic variants underlying these diseases. In psoriasis, such as the other complex diseases (hypertension, cancer, stroke, diabetes, atherosclerosis), continuously are published reports of conflicting genetic linkage and association claims, and it became mandatory to review the actual study design and find alternative and powerful tools for mapping susceptibility genes. In particular we would like to outline that limited results have been obtained by analyzing a single gene/locus in a single, specific, disease. An alternative strategy could be pooling the evidences. This approach can be addressed in several different ways. For example, we can pool the evidences arising from a combined genetic analysis of different disorder sharing clinical or pathogenetic features. This is the case of autoimmune or immuno-mediate diseases, occurring in 3-5% of the population and characterized by the specific organs attacked by the immune system. A common feature of all common diseases is the attack upon or the destruction of self by the immune system (56;77;78) and genomewide linkage analysis have confirmed that autoimmune diseases share susceptibility loci and conserved alteration in the expression of a common set of genes (56). In particular, a combined approach to investigate gene-expression patterns or association with specific gene variants in different disorders, could lead to a

Table 1. Common genes linked to multiple disorders

Chromosome localization	Disease	Gene	Reference
2q33	AIDT, IDDM, CD, RA	CTLA4	77, 78, 79, 80, 81
16q12	IBD,PSA	CARD15	73, 82
5q31	IBD, RA, ASTHMA	SLC22A4/SLC22A5	83, 84, 85
2q37	SLE, IDDM	PCD1	86, 87, 88
17q25	PS, SLE, RA, IBD	RUNX1 (binding site)	42, 87, 89

AIDT: autoimmune thyroiditis; IDDM: type I diabetes mellitus; CD: celiac disease; RA rheumatoid arthritis ; IBD: inflammatory bowel disease; PSA: psoriatic arthritis; SLE: systemic lupus erythematosus ; PS psoriasis

easier identification of common susceptibility genes (Table 1). This approach could pass up the limits originating from genetic heterogeneity, absence of a data replication, low penetrance of disorders.

Alternatively or in addition, we can pool the evidence by collecting a large set of patients both familiar and sporadic originating from different countries. This approach have been proposed and performed in psoriasis through the generation of the International Psoriasis Consortium, which collects and analyzes thousand of patients originating from all the most important research groups in the field. To date, this approach seems be the only one which can detect the small effect of secondary alleles and the low-penetrance variances with population specific effects. However, even if standardized protocols and analysis parameters are used, it should be outlined that the frequency and distribution of risk factors (both genetics and environmental) may well differ among patients belonging to different populations. On the other hand, pooling samples can enable investigators to subdivide the samples into relatively more homogeneous subgroups (endophenotypes) with size statistically significant.

In psoriasis, future tasks include identification of all predisposing genes in order to understand the molecular background and pathogenesis. This, in turn, will eventually lead to the development of better diagnostic tools, individually targeted treatment strategies, and better prognosis.

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