Genetics

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Content

Key Features

- Psoriasis attributes its manifestation to both genetic and environmental factors.
- Consensus has not been established as to the susceptibility allele for psoriasis.
- The genetic foundation responsible for psoriasis variability has proven difficult to decipher.

Psoriasis has been classified as a multifactorial disease. Multifactorial diseases attribute their manifestation to both genetic and environmental factors. The inheritance pattern of psoriasis is not that of a standard single-gene Mendelian pattern of inheritance. Instead, studies have demonstrated that among monozygotic twins,

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65–70 % concordance exists, and, among dizygotic twins, 15–20 % concordance exists (Farber). If psoriasis was a purely genetically inherited disease, the concordance of monozygotic twins would have approached 100 %. Thus, because the concordance does not show complete penetrance, this is evidence pointing towards other mechanisms of acquiring the disease. Environmental factors include stress, trauma, and infections such as streptococcal pharyngitis [1–3].

Early elucidation of genetic mechanisms relied heavily upon establishing familial patterns of inheritance. A thorough family history was taken, a pedigree chart was formed, and, based on trends of phenotypic expression by individuals, the geneticist would determine if the inheritance was autosomal dominant, autosomal recessive, x-linked, mitochondrial, or another form. Now with the advancement of molecular biology, microsatellite markers can be utilized to determine the pattern of inheritance through their positioning within DNA sequences and identification utilizing specific, commercially developed primers. Microsatellites are sequences of DNA often 1–6 base pairs in length that are repeated within the genome at different locations. These repeats arise from errors in DNA replication called replication slippage, which results in either expansion or contraction in the number of repeats. Often the number of repeats is maintained constant during inheritance between parent and offspring. Primers are used to test individuals within a family demonstrating the phenotype in order to establish putative susceptibility genes and/or alleles in a process known as linkage-based approach. Typically this method is successful for single-gene diseases and less successful for complex diseases such as psoriasis because it involves multiple loci with complex interactions. Another complication is the necessity of a large number of subjects which has been difficult to obtain without an established central database consisting of all individuals phenotypically expressing psoriasis.

Although the linkage-based approach does not contribute much to the determination of pathogenesis of psoriasis, it has provided putative loci for the disease. As technology has improved, better methods have been developed that are capable of comparing two groups: (1) persons with disease and a suspected allele versus (2) those without disease and without the said allele. This method is known as an association study, where microsatellites and single nucleotide polymorphisms (SNPs) are used to analyze a genome within and around a putative susceptibility locus or candidate gene. A SNP is a mutation arising from a substitution, deletion, or insertion of one nucleotide that exists in more than 1 % of the population. From the results, putative loci or genes can then be compared against regions that were proposed via the familial linkage-based approach. The existing setback for such a study is again the number of available subjects with the disease, the involvement of multiple genes, and the financial cost of testing subjects.

Consensus has not been established as to the susceptibility allele for psoriasis. Studies via linkage-based loci have universally confirmed the possibility of the susceptibility allele being present within the locus PSORS1 (a 300-kb region which extends from the HLA-B gene and includes the HLA-C gene) and involving the HLA-C gene located on chromosome 6p21. New developments greatly favor HLA-Cw*0602 as the susceptibility allele at locus PSORS1. This allele suggests

that cytotoxic killer T lymphocytes (CD8+ T lymphocytes) are likely to be involved in autoantigen recognition in psoriasis. T cells are thought to recognize epidermal keratin peptides, presented in the context of the Cw6 protein. As psoriasis is a multifactorial disease which involves multiple genes with unpredictable interactions, this complicates understanding the genetic mechanism of inheritance. To date, there are at least 20 genetic loci that have been identified from linkage-based studies. The following is a synopsis of existing literature on the genetics of psoriasis.

Although the susceptibility allele proposed to be located within PSORS1 has been supported by genome-wide linkage and association studies in unstratified trials, when stratifying patients it has been found that several additional loci have suggested involvement. Stratifying patients is a means of adjusting for confounders in epidemiologic studies. Studies stratifying patients according to age of disease onset, site of onset, presence of psoriatic arthritis, and nail involvement led to the strong suggestion of several other PSORS loci in the inheritance of psoriasis.

The PSORS2 locus found on chromosome 17q has been reported, but the location of the risk allele within this locus has been variable from study to study. It may be possible that there is more than one risk allele in this region [4]. PSORS3 was reported on chromosome 4q34, carrying a gene for a protein that regulates the production of *type 1 interferon*. Other studies have shown that type 1 interferon-deficient mice develop psoriasis-like skin lesions. When an association of early-onset psoriasis was seen with this gene, it made it a likely candidate for a susceptibility allele [5]. PSORS9 was reported on 4q31. Several genes reside within this region, and many code for *immunologic proteins*, such as interleukin 15. Antibodies against interleukin 15 have since been successfully tested as treatment on the psoriatic xenografts of mice [6]. PSORS4 resides on chromosome 1q21. It is found within the gene complex involved in *epidermal differentiation*. The genes in this complex encode S100 proteins. S100 proteins are involved in *leukocyte chemotaxis* and are upregulated in the keratinocytes of certain individuals with psoriasis who show linkage to the 1q21 locus [7]. Yet to be confirmed are PSORS5 on chromosome 3q21 and PSOR6 on chromosome 19p13. PSORS6 contains a gene called JUNB [8]. The JUNB is a member of the AP-1 transcription factor family, which controls the *differentiation of keratinocytes*.

The technology of high-volume SNP genotyping has allowed for the creation of extensive catalogs of SNP polymorphisms and LD blocks. As a result, population-based maps of LD haplotypes have been formed. In 2002, the International HapMap Project was launched. The goal of this project is to identify genetic variations between individuals at the population level. By defining subsets of highly informative SNPs ("tag" SNPs), the project aims to identify common patterns. Once more information on tag SNPs becomes available; researchers will then be able to use them in order to locate disease-associated alleles. This curtails the need to use up to ten million SNPs for genome-wide assays and will allow for more efficient genotyping. This approach will likely be used to help identify the remaining susceptibility and disease-modifying alleles in psoriasis.

As mentioned previously, the genetic foundation responsible for psoriasis variability has proven difficult to decipher. Even less is known as to the genetics of nail

psoriasis. Many patients with psoriasis experience nail changes, currently estimated at nearly half of all psoriasis patients [9]. More specifically, the subset of patients with psoriatic arthritis have a higher association with experiencing nail changes [10–15]. These nail changes include pitting, "oil drop" spotting, and onychodystrophy. A genetic cause for nail changes has not been verified, yet Julia et al. have identified a variation located at IL1RN that may be responsible for the nail trait in cutaneous psoriasis patients [16]. IL1RN – a regulator of IL-1A proinflammatory activity – has been shown to cause nail changes in children similar to those experienced by psoriasis vulgaris patients [17].

References

1. Gudjonsson JE, Elder JT. Psoriasis. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AM, Leffell DJ, editors. Fitzpatrick's dermatology in general medicine, vol. 1. New York: McGraw-Hill; 2007. p. 169–94.
2. Lomholt G. Psoriasis: prevalence, spontaneous course, and genetics. In: Published Ph.D Thesis (Lomholt G, ed), Copenhagen: G.E.C. GAC; 1963.
3. Watson W, Cann HM, Farber EM, Nall ML. The genetics of psoriasis. Arch Dermatol. 1972;105:197–207.
4. Samuelsson L, Enlund F, Torinson A, et al. A genome-wide search for genes predisposing to familial psoriasis by using stratification approach. Hum Genet. 1999;105:523–9.
5. Foerster J, Nolte I, Schweiger S, et al. Evaluation of the IRF-2 gene as a candidate for PSORS3. J Invest Dermatol. 2004;122:61–4.
6. Sagoo GS, Tazi-Ahnini R, Barker JW, et al. Meta-analysis of genomewide studies of psoriasis susceptibility reveals linkage to chromosomes 6p21 and 4q28-31. J Invest Dermatol. 2004;122:1401–5.
7. Coto E, Santos-Juanes J, Coto-Segura P, Alvarez V. New psoriasis susceptibility genes: momentum for skin-barrier disruption. J Invest Dermatol. 2011;131(5):1003–5.
8. Zenz R, Eferl R, Kenner L, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature. 2005;437:369–75.
9. Elder JT, Bruce AT, Gudjonsson JE, Johnston A, Stuart PE, Tejasvi T, Voorhees JJ, Abecasis GR, Nair RP. Molecular dissection of psoriasis: integrating genetics and biology. J Invest Dermatol. 2010;130:1213–26.
10. Baker H, Golding DN, Thompson M. The nails in psoriatic arthritis. Br J Dermatol. 1964;76:549–54.
11. Eastmond CJ, Wright V. The nail dystrophy of psoriatic arthritis. Ann Rheum Dis. 1979;38:226–8.
12. Gladman DD, Anhorn KA, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. J Rheumatol. 1986;13:586–92.
13. Lavaroni G, Kokelj F, Pauluzzi P, Trevisan G. The nails in psoriatic arthritis. Acta Derm Venereol Suppl. 1994;186:113.
14. Williamson L, Dalbeth N, Dockerty JL, Gee BC, Weatherall R, Wordsworth BP. Extended report: nail disease in psoriatic arthritis – clinically important, potentially treatable and often overlooked. Rheumatology. 2004;43:790–4.
15. Wright V. Psoriatic arthritis: a comparative study of rheumatoid arthritis and arthritis associated with psoriasis. Arch Dermatol. 1959;80:27–37.

16. Julia A, Tortosa R, Hernanz JM, Canete JD, Fonseca E, Ferrándiz C, Unamuno P, Puig L, Fernandez-Sueiro JL, Sanmarti R, Rodgriguez J, Gratacos J, Dauden E, Sanchez-Carazo JL, Lopez-Estebaranz JL, Moreno-Ramirez D, Quiero R, Montilla C, Torre-Alonso JC, Perez-Venegas JJ, Vanaclocha F, Herrera E, Munoz-Fernandez S, Gonzalez C, Roig D, Erra A, Acosta I, Fernandez-Nebro A, Zarco P, Alonso A, Lopez-Lasanta M, Garcia-Montero A, Gelpi JL, Absher D, Marsal S. Risk variants for psoriasis vulgaris in a large case-control collection and association with clinical subphenotypes. Hum Mol Genet. 2012;21:4549–57.
17. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerhoff A, Laxer R, Tedgard U, Cowen EW, Pham TH, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med. 2009;360:2426–37.