Research

My long-standing interest in psoriasis (Ps) continues; my first publication in this field was in 1975 Krueger GG, et al: Long-term maintenance of psoriatic human skin on congenitally athymic (nude) mice. J Invest Dermatol 64:307-312, 1975. In the 40 years since this publication, my research has remained focused on Ps. Changes in approaches to understand Ps have been necessary; the biggest change, Ps and its phenotypic variants have made it be a complex multigenic disorder. This means appreciating that 80% of the elements that drive the variable expression of Ps, have a genetic basis. This plus the realization that the mapping of the human genome was soon going cause us, in 2001, to begin the processes needed to discover how unique clinical phenotypes are genetically driven, e.g., ½ whose Ps gets better with every pregnancy; the ¼ of subjects with psoriatic arthritis (PsA), with phenotypic variants, spine vs small joints of hands, see (a) and (b) of figure and does not onsets until for some 10 years after the onset of Ps; the ¼ with widespread Ps and the ¼ who develop disabling Ps of palms and or soles, see (a) and (b) of figure. Restated our overall objective became what are the genes/gene-sets that associate with or are causative of these unique manifestations of Ps.

This challenge caused Kristina Callis Duffin, MD and myself to start the Utah Psoriasis Initiative (UPI) in 2003. To date we have enrolled over 1600 subjects with Ps in the UPI. Standardized entry data and exam as well as DNA have been collected on all subjects. Data from historical and physical phenotypic observations of those enrolled in the UPI are being used to test the hypothesis: clinical stratification of Ps by phenotype and by family association enhances identification of genetic factors driving specific elements of this disease. A third faculty has joined us, Jessica Walsh, MD a rheumatologist in 2010 she had spent 3 years preparing to offer the type of clinical expertise the UPI offers for the skin component of Ps for those who suffer from psoriatic arthritis. In the past 9 years we have seen the approach of genes/gene-sets that associate with or are causative of these unique manifestations of Ps begin to come to fruition, see references.

To gain further insight into the genetic architecture of Ps four projects have been undertaken. (A) We added our cases to a meta-analysis of three genome-wide association studies (GWAS) and two independent datasets genotyped on the Immunochip, 10,588 cases and 22,806 controls in total. This led to the discovery of 15 novel disease susceptibility regions in the pathway that drives the innate immune response, increasing the number of Ps-associated loci to 36 for Caucasians, ref 7. (B) The UPI joined the team led by JT Elder and Goncalo Abeçasis in a U01 NIH funded project to sequence through the highly significant (p≤10^{-8}) disease associated loci by the Baylor group to discover the causative polymorphism(s) from 5000 cases and controls. Sequencing was directed at the exomes of 7 genes with the strongest association with Ps. This is completed; data are in house. (C) Exome-XX features a chip developed for Ps by Affymetrix with collaborators at the Univ of Michigan. The core of this chip has 586,000 genetic variants including coding SNPs and indels, GWAS and pharmacogenomic variants, eQTLs, loss of function markers, variants in regulatory regions, markers for autoimmune diseases. In addition it features 70,320 SNPs that identify loci that associate with Ps. The UPI contributed 1200 cases and 1200 controls; all have gone through this exome array genotyping experiment and Ps specific SNPs; data are in house. (D) Most recently our group, led by colleagues at the U of Michigan, have used the PsA phenotype for fine mapping of genetic risk factors for PsA, comparing PsA with cutaneous-only psoriasis (PsC, defined as having Ps only for > 10yrs, i.e., unlikely to ever get PsA). This was a
Research Service Project: Ps a complex multigenic disorder: where is the missing heritability?

To date GWAS studies demonstrate that less than 35% of the heritability of Ps is explained by association loci has been discovered. We have initiated a program directed at discovery of the missing heritability. With Bingjian Feng PhD of our Dept. and the Utah Genome Project (UGP) we have embarked on a case/case approach where we identify via the Utah Population Data Base large families with psoriasis. Over 50 such families with more than 20 affected have been identified. The plan is to do genomic sequencing of first and second cousins affected with Ps, (they share 1/8 and 1/16 of DNA) in these pedigrees. We posit that sharing of DNA will lead to the discovery of loci that harbor polymorphisms that maybe unique to their psoriasis and phenotype. Early data tell us this is a very solid approach. Lessons learned will be applicable to other complex-multigenic disorders and will do much to bring Utah back to center stage for the discovery of these disorders. Funds for this have come from my Benning Endowed Chair and the Utah Genome Project.

Biographical Summary

Education and Professional Experience: Undergraduate in Chemistry at Union College (1958-62); MD in Loma Linda University (1962-1966); Internship, Fitzsimmons Army Hospital (1966-67); Military Service US Army 82nd Airborne General Medical Officer (1967-69); Residency in Dermatology University of Colorado Medical Center, Denver (1969-72); Faculty Member University of Utah, Department of Medicine, Head and Founder Division of Dermatology (1972-1996).

Current Professional Service: Professor of Dermatology University of Utah, 1996 to current, HA & Edna Benning Presidential Endowed Chair 2006 to current; Executive Committee, Dermatology Foundation 1988 to current.


From CV > 200 publications, selected from 26 publications after UPI reached maturity 2005