

In This Issue: Genes Everywhere for Everything

Lowell A. Goldsmith, Chapel Hill, North Carolina, USA

Francis Bacon (1561–1626) wrote “As Physic advances farther and farther every day and develops new axioms, it will require fresh assistance from Mathematic.” So right. Modern genetics gathers its data from patients, their families, gels, and robotic analyzers, using mathematical and statistical techniques to analyze complex data and the interactions between genetics and environment. The mathematics must not be off-putting, and it should be considered as just another scientific technique.

Just as most readers do not perform every laboratory procedure they read about, they don't have to derive the equations or recrunch the data from statistical reports. However, they do need to know the basic principles and why one analytical technique may be more useful or powerful than another in various circumstances. In this issue the readers can sample from a rich bouillabaisse of genetic findings and techniques.

Complicating the Straightforward: Cystic Fibrosis and XP

For the dermatologist, cystic fibrosis usually conjures salty sweat associated with early death and skin changes related to nutritional deficiencies. This severe, relatively common (1:2000–1:3000 births) autosomal recessive disorder often has associated pancreatic disease with malabsorption and meconium ileus, as well as congenital malformation of the reproductive tract and a decreased life expectancy. Some cases of “idiopathic pancreatitis” or bilateral absence of the vas deferens are related to deficiencies in the cystic fibrosis gene. The deficient gene is CFTR (cystic fibrosis transmembrane conductance regulator), a member of the ATP-binding cassette (ABC) transporter family of membrane proteins.

Sato and coworkers (p. 1224) determined that CFTR protein and its message normally are present in the epidermis immunohistologically, using in situ hybridization and RT-PCR (reverse transcription-polymerase chain reaction) techniques. Living epidermal cells contain the protein, as do sweat duct secretory cells. In mucosal tissues CFTR mutation contributes to abnormal glandular function and deficient antimicrobial activity. CFTR's role in epidermis is not as clear, but will no doubt be investigated with knock-out animals, including skin specific knockouts, and more careful study of the skin of patients with the disease.

While CF is a common, albeit recessive, genetic disorder, Xeroderma Pigmentosum is rare (incidence usually given as 1:1,000,000). Rare diseases often have more publications associated with them than there are patients with the disease (Since 1966

there are 2999 references in Medline for XP and 4923 references for acne, for comparison). The importance of XP for understanding basic mechanisms of UV damage, repair and carcinogenesis, however, cannot be overemphasized. The UV induced tumors in XP have characteristic UV-induced mutations in p53, but Bassett-Seguín and colleagues also unexpectedly found a germline mutation in the cell cycle control gene INK4a-ARF, which codes for p16^{INK4a} and p14^{ARF}, two cell cycle control proteins in skin tumors in the basal cell carcinomas. Remarkably, an XP patient also expressed a germline mutation in p16^{INK4a}. The XP patient had complementation type C, the most common form of XP, by genetic and complementation analysis, with severe photosensitivity, actinic keratoses, squamous cell carcinomas and basal cell carcinomas beginning at age 4. At age seven he developed a T cell lymphoblastic lymphoma and at age 10 an atypical fibroxanthoma and epithelioid hemangioma.

The germline mutation was determined by its presence in normal skin and a fibroblast line. The interaction of these two mutations, p53 and p16^{INK4a}, may have had a role in the lymphoma and unusual skin malignancies, as discussed by the authors. This suggests the usefulness of careful and detailed studies of unusual malignancies in XP patients and shows the importance of genetic studies in malignancies. The interactions and possible synergy between these two abnormal genes may represent an important disease model.

SKIN TUMORS

Keratoacanthomas: disappearing malignancies

Squamous cell carcinomas never go away, and most keratoacanthomas (KA), although cellularly atypical, regress. This interesting biological phenomenon of regression has now been studied on the genetic level (p. 1367). Using techniques which allowed scanning of all chromosomes for about 1/3 of immunosuppressed and non-immunosuppressed patients, Clausen and coworkers showed genomic abnormalities including gains (duplications of chromosomal regions), and deletions. In squamous cell

carcinomas there were some shared types of genomic lesions and aberrations present in KA. There was a trend but no strong correlation between atypia in KA and genomic lesions. The techniques used were more general than loss of heterozygosity for particular regions; hence, there can be fewer assumptions about why these regions may be altered. Similar studies identified regions associated with the phenotypic variability of tumor regression.

Antipodal solar keratoses

Sun, sun, sun is our image of Australia, and 50% of Australian Caucasians over 40 have solar keratoses (SK). In this rich field of keratoses Carless and coworkers (p. 1373) studied the role of glutathione-S-transferase (GST) polymorphisms and SK. The GST enzymes play a role in detoxifying carcinogens and mutagens, including UV-induced mutations. In a case-control study, one of the four GST alleles (GSTM1) was associated with an increase in SK development, especially when associated with outdoor exposure. The strength of this association was smaller than, and confounded by fair skin and the inability to tan – two common traits, in the Celtic-derived Antipodal people. A previous study by

the same group had failed to show a relationship with GST polymorphisms and, in retrospect, the authors believe that study did not have a large enough population to show a difference. Furthermore, follow-up on the “non-affected” from the earlier study showed that many of them developed SK. The current study shows the opportunity and challenge of doing properly powered studies, having a valid control (especially for time-dependent lesions like SK), and the utility of going back to a study group after a period of time for re-study. Detailed mechanisms of GST and its polymorphisms and skin cancer will continue to be of interest.

Common disease-role of genetics: Acne and Psoriasis

Bataille and co-workers studied Caucasian women from a London-based registry, and gathered together 458 pairs of monozygotic (MZ) and dizygotic (DZ) twins over a three-year period to study the relative contribution of genetic and environmental factors on the liability to acne. Twin studies are very useful in studying common genetic diseases; the rationale is simple: the more genetics plays a role in disease etiology, the higher the concordance for pairs of MZ twins than the concordance for same-sex DZ twins. There was a similar prevalence (14%) of acne reported by DZ and MZ, and recall bias was considered to have a role in the lower-than-expected prevalence, as the average age of patients studied was 46 years and milder degrees of acne may not have been reported. Detailed genetic modeling was performed, which suggested that 81% (95% CI: 73–87%) of the variance could be attributable to additive genetic factors and the remaining 19% to unshared (i.e., environmental) factors. This study would certainly allow chocolate stocks to rise dramatically, and suggests that gene mapping for acne may yield useful candidate genes (p. 1317).

The genetics of psoriasis is a growth industry and an interesting study comes from Zhang and colleagues (p. 1361). Chinese

Hans, the predominant national (ethnic) group representing 92.5% of the Chinese population (2000 census), were studied. Previous studies suggest a prevalence of psoriasis of 0.123% in China, which is much lower than the prevalence of about 2% usually reported for Europe and the United States. Families with more than one member with psoriasis were studied with standard gene mapping techniques. The mean age of onset was 23.8 years in the Hans. Not surprisingly, the PROSI locus, on the short arm of chromosome 6 at 6p21, which is near HLA, was positively associated with the disease. As might be suspected in a new ethnic group study, there was a new locus identified on the long arm of chromosome 4 in the Han population, different in location from the previously-identified chromosome 4 locus found in other studies. In the Han population, and with the size of their study, the authors were not able to replicate the linkage with other chromosome regions which have been identified in other populations and studies. Studies of other Han populations, in other countries, could replicate these results and identification of the new genes associated with psoriasis. (p. 1361)