This Month in the *Journal*

The lack of reproducibility for genetic analyses of prostate cancer has been a frustrating aspect of this field. This month in the *Journal,* Elaine Ostrander and Janet Stanford have contributed a review (p. 1367) in which they discuss the lessons that researchers have learned from studies of prostate cancer genetics. They also provide an outline of the challenges facing this field, including genetic heterogeneity and phenotype variability. Although progress in this field has been slow, the recent cloning and confirmation of the *HPC2/ELAC2* locus for prostate cancer (see the review's citations of work by Tavtigian et al. and Rebbeck et al.) give hope that the tide is turning.

Also in this issue is an editorial by Jeff Lell and Doug Wallace (p. 1376) on the peopling of Europe. They discuss recent work by Richards et al. (in the November 2000 issue [p. 1251–1276]) and by Rosser et al. (in this issue [p. 1526]), who have used mtDNA and Y chromosomes, respectively, to study genetic lineages in Europe. Through these studies, the influences that such factors as geography, language, and migration have had on the history of Europe have been further explored. Although, because of the different methods used, it is difficult to make direct comparisons between the two papers, both works provide some support for the spread of agriculture via migrations of Near Eastern farmers into Europe during the Neolithic.

FOXC2 ***Mutations in Lymphedema-Distichiasis,*** *by Fang et al.* **(***p. 1382***)**

Through use of a patient with a t(Y;16)(q12:q24.3) that is associated with neonatal lymphedema, Fang et al. have been able to identify the gene for lymphedema-distichiasis (LD) as the *FOXC2* gene. LD is an autosomal dominant disorder in which affected individuals have double rows of eyelashes (distichiasis) and lymphedema in the limbs. Several other tissues may be affected, leading to cleft palate, extradural cysts, and cardiac and spine defects. Although no open reading frames crossed the translocation breakpoint in their proband, the authors speculated that a position effect was altering the expression of distant genes. Three forkhead gene–family members were found in the region near the breakpoint. *FOXC2* was the most likely candidate gene, since it is known to play a role in the development of several different tissues in mice. Sequencing revealed *FOXC2* mutations in two other LD families—a nonsense mutation that truncated FOXC2, within the conserved forkhead domain, and a 4-nucleotide frameshift mutation, located after the forkhead domain, that also truncated the protein. Taken together, the mutations suggest that haploinsufficiency of *FOXC2* leads to LD. These results provide further information concerning the role that *FOXC2* plays in human development.

Jejunal Cl^- Section in Cystic Fibrosis, *by Högenauer et al.* **(***p. 1422***)**

The high carrier frequency for cystic fibrosis (CF) mutations has led many to speculate that there is a heterozygote advantage for these mutations. A likely selective force for the CF transmembrane-conductance regulator (CFTR) is secretory diarrhea, since this secretion is mediated by the CFTR Cl^- channel. A reduction in Cl^- secretion by the CFTR channel is predicted to reduce the likelihood of dehydration through diarrhea. In fact, some studies have indicated that mice heterozygous for a CFTR mutation do show a reduced intestinal secretion rate in response to cholera toxin, a classic inducer of secretory diarrhea (see Högenauer et al.'s citations of work by Gabriel et al.). Other labs have not seen the reduced secretion in heterozygous mice, so this hypothesis is controversial. In an attempt to quell this controversy, Högenauer et al. have measured intestinal secretion in patients with CF and in their carrier parents. As would be expected, the individuals with CF had no active Cl^- secretion in their jejunums, even in response to a prostaglandin analog. In contrast, their heterozygous parents had levels of Cl^- secretion that were similar to that measured in normal individuals. These data do not support the hypothesis that carriers of CF are protected from dehydration due to secretory diarrhea. They do, however, show that CFTR expression is not rate limiting for active Cl^- secretion in CF heterozygotes.

Genetics of Thrombosis: The GAIT Study, *by Souto et al.* **(***p. 1452***)**

Most of the genetic information that we know about thrombosis has been gleaned through association studies. To get at this problem from a different angle, Souto et al. have performed a large family study on thrombosis, to determine the genetic heritability of this disorder as well as to examine the correlations between quantitative risk factors and thrombosis. Surprisingly, they report that >60% of the variation in susceptibility to thrombosis is due to genetic factors. In addition, they find strong genetic correlations between thrombosis and the levels of factor VIII, factor IX, factor XI, von Willebrand

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factor, activated protein C ratio, homocysteine, and tissue-plasminogen activator, indicating that thrombosis may have genetic influences in common with these physiological parameters. If their models are correct, this work opens the door to the discovery of quantitative-trait loci that contribute to the risk of thrombosis.

LD Physical Distance and Population History, *by Dunning et al.* **(***p. 1544***)**

Just how many SNPs *will* it take to allow us to perform a complete genome scan for disease association? Dunning et al. have attacked this question, the current scourge of genome research, by comparison of linkage disequilibrium (LD) between genetic regions and between ethnic populations. In the study, they used markers with minor-allele frequencies >.1, in order to make them comparable with common disease-susceptibility polymorphisms. The four populations that they have studied have strikingly different population histories and include East Anglian British, Afrikaners, Ashkenazim, and Kuopio Finnish. In contrast to what has been predicted by other groups, little LD difference was seen between the populations, making it unlikely that the use of any one of these populations will be unusually advantageous in disease association studies. They also find that LD declines rapidly with distance but is detectable for markers up to 500 kb apart. An assessment of the number of marker pairs that show LD amounts that, on the basis of required sample sizes, would be useful in association studies revealed that 50% of marker pairs 5 kb apart did not have sufficient LD for these studies. At 20–50-kb spacing, almost none of the markers would be useful. Since their calculations are based on three chromosomal regions, their data may not reflect the LD across the genome, but this work moves us toward a greater understanding of the LD/distance relationship.

HED, Immunodeficiency, and* IKK-gamma *Mutations, *by Zonana et al.* **(***p. 1555***)**

Zonana et al. define a new X-linked syndrome characterized by immunodeficiency and hypohidrotic ectodermal dysplasia (HED-ID). Affected males exhibit dysgammaglobulinemia, abnormal dentition, difficulty in sweating, and sparse scalp hair. Affected males in four families were found to have mutations in the most 3′ exon of *IKK-gamma,* a gene that encodes a protein involved in NF-κB activation. This makes HED-ID allelic to another ectodermal dysplasia, incontinentia pigmenti (IP). In contrast to HED-ID, IP is almost always lethal to males. Females with IP have a variety of defects of the brain, skin, hair, teeth, and eyes. The dominant nature of IP appears to result from a complete loss of IKK-gamma activity, whereas a partial loss of activity leads to the less severe, HED-ID phenotype. It remains to be seen how the other proteins that are associated with HED phenotypes tie in to the IKK-gamma/ NF-κB signaling pathway.

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