This Month in the *Journal*

IGF2 *in First Cousins,* *by Sperandeo et al.* **(***p. 841***)**

Klippel-Trenaunay-Weber syndrome (KTWS) is a disorder that is of unknown etiology and that is characterized by cutaneous hemangiomata with hypertrophy of related bones and soft tissues. Sperandeo et al. present a proband with KTWS whose first cousin is affected by Beckwith-Wiedemann syndrome (BWS), and they provide evidence for related epigenetic alterations in the two patients. Although the probands possess different alleles across the 11p15.5 region, which is implicated in BWS, they show relaxed imprinting and biallelic expression of *IGF2,* a growth-factor gene in this region. These results exclude a common genetic defect in this region but suggest that the two syndromes may be related through a common epigenetic alteration. A mutation in a gene unlinked to 11p15.5 may have caused epigenetic alterations in both cousins, including the relaxed imprinting at *IGF2*. Since both diseases are syndromes of overgrowth, overexpression of the IGF2 growth factor, due to relaxed imprinting, is likely to play a role in disease development. Phenotypic differences in these disorders may have resulted from additional and unique epigenetic alterations, including differential methylation at the *KvDMR1* locus, which was identified in the cousins.

Elastogenesis in Costello Syndrome, *by Hinek et al.* **(***p. 859***)**

Costello syndrome is one of a group of disorders, also including Hurler, Marfan, and William syndromes, that result from the disruption of elastic fiber production. Individuals with Costello syndrome exhibit several remarkable features, including short stature, mental retardation, and a characteristic appearance. Their soft skin is excessively creased on the palms and soles. Although elastin deposition is impaired in the skin of these individuals, the defect occurs at a step post transcription. In this article by Hinek et al., elastogenesis in the cells of patients with Costello syndrome is found to be impaired because of a deficiency of elastin-binding protein (EBP), a chaperone that brings tropoelastin to its site of extracellular assembly. Although fibroblasts from patients with Costello syndrome produce EBP at wild-type levels, the protein is quickly lost to the media, rendering tropoelastin cell bound and susceptible to degradation. The shedding of EBP is associated with abnormal lysosomal accumulations of chondroitin sulfate–bearing moieties, which disrupt the association of EBP with tropoelastin and cell membranes. The defect in elastogenesis is reversed by the addition of chrondroitinase ABC to degrade the chondroitin sulfate–bearing proteoglycans. Hinek et al. propose that accumulation of chondroitin sulfate–bearing moieties, due to impaired degradation, leads to shedding of EBP from the cells, preventing EBP from performing its role in elastogenesis. This defect in elastin production, along with its consequent increase in the rate of cell proliferation, may lead to the phenotypic features of Costello syndrome. Recent findings implicate a similar mechanism in the development of Hurler syndrome, a disorder with phenotypic similarities to Costello syndrome. In Hurler syndrome, accumulation of dermatan sulfate, another galactosugar-bearing moeity, is associated with impaired elastogenesis.

New Loci for Recessive Icthyosis, *by Fischer et al.* **(***p. 904***); *Netherton Syndrome Maps to 5q32,* *by Chavanas et al.* **(***p. 914***);** *and* ***Report* (*The Third ARCI Locus on Chromosome 19p13.1-2*),** *by Virolainen et al.* **(***p. 1132***)**

Congenital ichthyosis is a keratinization disorder that causes scales to form on the skin. There are several forms of ichthyosis, found either as distinct disease entities or as part of a disease syndrome. Autosomal recessive, lamellar ichthyosis has been linked to two loci, one on chromosome 14q11 and one on chromosome 2q33-q35. The responsible gene on chromosome 14 has been identified as *TGM1,* which encodes keratinocyte transglutaminase, an enzyme that catalyzes the formation of the cornified cell envelope. Many patients affected with autosomal recessive ichthyosis do not show linkage to either of these loci, so further analysis has been performed. Both Virolainen et al. and Fischer et al. find linkage of congenital ichthyosis to chromosome 19p, although the manifestations of this disease are different in the two sample sets. Although the patients in the Fischer et al. study have symptoms of lamellar ichthyosis with large, brownish adherent scales, the subjects in the Virolainen et al. study have a nonlamellar phenotype and present with fine, white scales. In addition, Fischer et al. find linkage of an erythrodermic form of ichthyosis to chromosome 3p21. Chavanas et al. perform linkage analysis on patients with Netherton syndrome, a disorder characterized by congenital ichthyosis, and find that this syndrome is not linked to any of the known ichthyosis loci but, rather, to chromosome 5q32. These articles emphasize the genetic heterogeneity of the congenital ichthyoses; however, the causative genes are all likely to be

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those whose products are involved at various steps in epidermal differentiation.

Genome Screen of Prostate Cancer, *by Suarez et al.* **(***p. 933***)***; and* ***Combined Linkage Analysis of HPC1,*** *by Xu et al.* **(***p. 945***)**

Although there are certainly environmental and lifestyle factors that influence the development of prostate cancer, there is also a genetic component to the disease. Individuals with either multiple affected first-degree relatives or an affected brother with an early age at onset are at increased risk for development of prostate cancer. A small number of loci have been associated with an increased risk for prostate cancer, including *HPC1* on chromosome 1q24-25. Xu et al. (the International Consortium for Prostate Cancer Genetics [ICPCG] also is an "author"). and Suarez et al. have analyzed hundreds of families affected with hereditary prostate cancer, in order to examine further the genetics of prostate cancer. The ICPCG study supports linkage to the *HPC1* locus in a small percentage of these families, whereas the study by Suarez et al. identifies several regions—at chromosomes 2q, 12p, 15q, 16p, and 16q—with possible linkage to prostate cancer. Further classification of each population increased the evidence for linkage in certain subsets of each population. Confirming previous results, the ICPCG study found that the proportion of families showing evidence for linkage to *HPC1* was increased in sets of families with either male-to-male disease transmission, five or more affected members, or an early age of onset. Subdivision of the sample population studied by Suarez et al. revealed three additional regions of interest: families with a history of breast cancer showed evidence for linkage to chromosome 1q35.1; those without a family history of prostate cancer had linkage at a region proximal to *HPC1*; and those with a late age at onset had linkage to chromosome 4q. These studies underscore the complexity of prostate cancer and further suggest genetic heterogeneity for this disease. In addition, careful classification of affected families into different subgroups may help to identify genetic regions of interest.

mtDNA and Icelandic Origins, *by Helgason et al.* **(***p. 999***)**

Before its discovery by Vikings, circa 870 A.D., Iceland was uninhabited. Both the relatively recent colonization of this island and its isolation have given rise to a modern population of Icelanders that is descended almost entirely from the original founder lineages. Helgason et al. have used these unique properties to study the origins of the women who originally settled Iceland. Comparisons of mtDNA sequences from Icelandic people with those from other European peoples have allowed Helgason et al. to create one of the most extensive phylogenies of mtDNA lineages for a human population. In agreement with historical texts, Scandinavian and British populations were found to have contributed to the Icelandic gene pool. These texts claim that women and slaves were brought from Norse settlements in Britain and that some of these early settlers were actually captured during raids in Britain and then were brought to Iceland. The founding females did not carry a homogeneous set of mtDNA lineages, further suggesting a diverse founder population. Although sampling of Icelandic mtDNA lineages is near saturation and thus useful for these studies, numerous lineages in other European countries appear to remain undocumented. Further sampling of European lineages is required for accurate analysis of their genealogical relationships on the basis of mtDNA gene pools.

Relationship Testing, *by McPeek and Sun* **(***p. 1076***)**

The inability to identify misspecified relationships in linkage studies can result in either reduced power or false-positive evidence for linkage. McPeek and Sun present new methods that use genome-screen data to determine the accuracy of pedigree relationships. Their methods are suitable for analysis of more-general relative pairs than sibs and half-sibs, such as avuncular and first-cousin relationships. Two new test statistics are proposed: conditional expected IBD (EIBD) and adjusted IBS (AIBS). EIBD and AIBS are computationally more simple than previous tests; they do not require the specification of an alternative relationship; and they take into account chance sharing. These methods, when applied to a data set of 2,810 relative pairs from the Collaborative Study on the Genetics of Alcoholism, identified 26 relative pairs that include misspecified relationships. Some of the errors could not have been detected through analysis of sibs and half-sibs alone. Many of these discrepancies can be corrected with additional information from the involved pedigrees.

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