This Month in the *Journal*

This month in the *Journal,* Walter Nance and Michael Kearsey provide their thoughts on the role of the connexins in human evolution. Previous work from Dr. Nance's group suggested that the frequency of mutations at the *DFNB1* deafness locus, which includes the genes for connexins 26 and 30, has doubled in the United States in the past 200 years. Here, they performed simulations indicating that a combination of relaxed selection and assortative mating due to the development of sign language could have led to this rapid rise in the incidence of connexin-associated deafness. This got them to thinking about the evolution of speech in general. They propose that once the first mutations for oral communication arose, assortative mating based on linguistic homogamy may have played a role in the accelerated fixation of genes for speech.

CHEK2*1100delC and Susceptibility to Breast Cancer, *by The CHEK2 Breast Cancer Case-Control Consortium* **(***p. 1175***)**

The *CHEK2*1100delC* mutation abrogates the kinase function of this protein, which is involved in checkpoint control and DNA damage repair. This variant is associated with increased risk of breast cancer, but robust estimates of the relative risk it confers in the absence of family history are lacking. To further examine this association, members of the CHEK2 Breast Cancer Case-Control Consortium combined data from 10 case-control studies of CHEK2*1100delC, for a total of ~11,000 cases (that were unselected for family history) and 9,000 controls. The results of this population-based analysis indicate that carriers of CHEK2*1100delC have an approximately twofold increased risk of breast cancer, although the risk seems to be greater in women with affected first-degree relatives and in those diagnosed at younger ages. This risk is relatively modest compared with that conferred by mutations in *BRCA1* and *BRCA2*. At this point, the authors don't feel it is appropriate to routinely test for CHEK2*1100delC, which they estimate should only be responsible for ~0.7% of breast cancer cases, although this figure will vary according to the population frequency of the variant.

Human Y-Chromosomal Microsatellites, *by Kayser et al.* **(***p. 1183***)**

Y-chromosomal microsatellites are important markers used in forensic and phylogenetic studies. To date, only 53 are known, and this limits the resolution that can be achieved between lineages. Kayser et al. used the recently reported Y-chromosome sequence to find 166 novel microsatellites, thereby quadrupling the number of available markers. Of the novel markers, 139 were polymorphic in a sample of eight chromosomes from different haplogroups. Comparisons of the markers through multiple linear regressions allowed the authors to determine that repeat count—or, in the case of complex repeats, the repeat count of the longest homogeneous array—appears to explain a large proportion of the repeat variance in these markers. It is likely that the great majority of useful microsatellites on the Y chromosome have now been reported, thereby making it easier for researchers to select appropriate markers for high-resolution analysis of Y chromosomes.

MSH6 ***Germline Mutations,*** *by Buttin et al.* **(***p. 1262***)**

Although germline mutations in the mismatch-repair gene *MSH6* have been found in families with suspected hereditary nonpolyposis colorectal cancer (HNPCC), these families often do not meet the classic diagnostic criteria for this disorder, and many cancers in *MSH6* mutation carriers do not exhibit the expected high levels of microsatellite instability. This makes unclear the exact role of *MSH6* in susceptibility to inherited cancers. To address this question, Buttin et al. studied seven kindreds with *MSH6* germline mutations. The families were identified through probands with endometrial cancer who were ascertained independent of family history or age at diagnosis, and the authors gathered information on cancers in 278 of the probands' relatives. They found a significant excess of *MSH6* mutation carriers among the affected family members, indicating that *MSH6* germline mutations are associated with increased cancer risk. Further supporting this association is the fact that the rate of cancers in first-degree relatives of the probands with *MSH6* mutations is higher than in relatives of presumably sporadic cases of endometrial cancer. Including the probands, the overall penetrance of the mutations was close to 60%, which is higher than previously believed. It is unfortunate that it is not yet clear which families should be screened for *MSH6* mutations, because they are not necessarily associated with a family history of HNPCC, a young age at diagnosis, or microsatellite instability in the tumors.

0002-9297/2004/7406-0001$15.00

Offspring Gender and Miscarriages in BRCA1/2, *by Gal et al.* **(***p. 1270***)**

A recent article by de la Hoya et al. (see reference in Gal et al.) analyzed the sex ratio in 68 Spanish pedigrees with breast and/or ovarian cancer and found that, in the pedigrees segregating *BRCA1* mutations, there was strong skewing of the sex ratio (2:1) against males. This skewing was not seen in a sample of families with *BRCA2* mutations, nor in those without a detectable mutation in either gene. Gal et al. were interested in this finding and wondered whether similar results could be found in an Ashkenazi Jewish sample, which should have a high proportion of *BRCA1* and *BRCA2* mutations. As in the study by de la Hoya et al., all women in the sample of Gal et al. were at high risk of familial breast and ovarian cancer. Comparisons were made between those women with and those without the three predominant Jewish mutations in *BRCA1* and *BRCA2*. Unlike the study by de la Hoya et al., no difference in the male:female offspring ratio was observed, but an explanation for the conflicting results between the Spanish and Israeli Jewish populations is not clear. Because no homozygous *BRCA1/2* mutation carriers have ever been reported, despite relatively high mutation frequencies, Gal et al. also wondered whether the *BRCA1/2* mutation carriers in their sample had increased rates of recurrent spontaneous miscarriage that could represent inviability of homozygous fetuses. No differences in the rates of recurrent spontaneous miscarriage were found between mutation carriers and noncarriers. However, both groups had higher rates of recurrent miscarriage than have been reported for an average risk population, so additional follow-up in this area is needed.

Chromosomal Abnormalities, *by Winther et al.* **(***p. 1282***)**

The chemotherapeutic agents and radiation used to treat childhood cancers are capable of inducing mutations, but it is not absolutely clear whether treatment with these agents will affect the future children of cancer survivors. Winther et al. used the extensive Danish health care registries to do a population-based study of this problem. They found 4,676 cancer survivors in the Danish Cancer Registry who were diagnosed at age <20 years and who survived to the onset of fertility. By connecting this information with data from the Danish Cytogenetic Registry, Winther et al. could compare the rates of chromosomal aberrations in the survivors' offspring with those in the offspring of the survivors' 6,441 siblings. No differences in the proportions of liveborn children with chromosome abnormalities were observed, which should provide further reassurance to cancer survivors who are contemplating having kids.

Bias Dependent on Test Statistic Used, *by Cordell* **(***p. 1294***)**

In a recent article, Schork and Greenwood (Am J Hum Genet 74:306–316) suggested that nonparametric (model-free) linkage analyses can show a bias toward the null hypothesis of no effect because uninformative relative pairs are assigned expected allele-sharing values. This conclusion turned out to be quite controversial, because it was interpreted by some as a criticism of model-free analysis methods in general, especially since the authors suggested that researchers who have used these methods should revisit their results. In this issue, Heather Cordell examines the extent of this problem and shows that most of the test statistics available in standard linkage analysis packages (such as Genehunter, Merlin, and Allegro) are, in fact, not affected, because they do not assign expected allele-sharing values to uninformative relative pairs but rather allow for uncertainty in identity-by-descent sharing. She points out that the conclusions made by Schork and Greenwood result, in part, from the test statistic they chose to investigate. Schork and Greenwood admitted in their article that their simulation study was explicitly constructed as a worst-case scenario to demonstrate the bias. An examination of some of the more complex linkage methods for analysis of qualitative and quantitative traits showed that, although some statistics can be affected, methods exist in the literature to overcome the problem. Although this was not an exhaustive study, in terms of the statistics tested, this work should serve to clarify the situations in which the bias could be a concern.

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