This Month in the *Journal*

This month in the *Journal*, David Amor and Andy Choo provide an overview of neocentromeres. Despite the absence of centromeric α-satellite DNA, neocentromeres are able to assemble a functional kinetochore and function as de novo centromeres. The formation, composition, and consequences of neocentromere formation are discussed, as are their potential roles in gene therapy and in evolution.

Diallelic Indels, *by Weber et al.* **(*p. 854*)**

Weber et al. report the most comprehensive screen of human diallelic insertion/deletion (indel) polymorphisms to date, with 2,000 indels identified and characterized. The identification of a large number of indel polymorphisms is likely to be valuable for gene-mapping studies, and complete information on the indels described in this work will be available online (for details, see the "Results" section of the paper). Indels were identified through comparisons of overlapping human genomic or cDNA sequences. Attempts were then made to confirm the polymorphisms by amplifying the sequences from a variety of human populations and from at least one great ape sample. Approximately 58% of the candidate indels were actually confirmed. Through comparisons with the corresponding sequences from apes, it was found that nearly all of the indels arose since the divergence of the human, chimpanzee, and gorilla common ancestors and that the monomorphic alleles in chimps and gorillas are likely to represent the ancestral alleles. Examination of the indel allele frequencies allows some speculation on population histories. Whereas, in the African populations, newer indel alleles have a bias toward low allele frequencies, the European, Japanese, and Native American populations have undergone population bottlenecks, so there is less bias for new alleles to be at low frequency.

Neuregulin 1 *and Schizophrenia,* *by Stefansson et al.* **(*p. 877*)**

Starting with a sample of Icelandic individuals with schizophrenia, Stefansson et al. used the powerful Icelandic genealogy database to generate large multiplex pedigrees for use in a genomewide linkage scan that identifies *neuregulin 1* (*NRG1*) as a candidate gene for schizophrenia risk. This gene is located on chromosome 8p, a region that has been identified in other linkage studies for schizophrenia. A core risk haplotype that contains the first exon of *NRG1* was identified in the families, and it is estimated to increase the risk of schizophrenia by 2.2-fold, compared to the wild-type haplotype. Unfortunately, no obvious functional *NRG1* variant could be identified. The role of *NRG1* in schizophrenia is, however, supported by mouse models. Replicating what was seen in another strain of *NRG1* mutant mice, Stefansson et al. found that mice heterozygous for mutations in *NRG1* or *ErbB4* (a neuregulin receptor) show hyperactivity that can be reversed by treatment with the antipsychotic clozapine. The *NRG1* hypomorphic mice also showed impaired prepulse inhibition and a reduction in the number of functional N-methyl-D-aspartate (NMDA) receptors, both features that have been seen in schizophrenic humans. Although a conclusive role for neuregulin in the development of schizophrenia has not been demonstrated, *NRG1* is an interesting candidate gene for follow-up.

Y-Chromosome Palindromes and Massive Deletions, *by Repping et al.* **(*p. 906*)**

Repping et al. have characterized *AZFb* and *AZFb* plus *AZFc* deletions on the Y chromosome, and these turn out to be some of the largest human interstitial deletions for which the deletion junctions and intervening sequence are known. *AZFb* and *AZFc* are two of the three regions on the Y chromosome that are essential for normal spermatogenesis, and the deletions in this study were found in men whose only obvious phenotype was azoospermia (absence of sperm in the semen). This is surprising because of the number of genes (up to 42) removed by the deletions, including a number that are known to be expressed in tissues other than the testes. Homologous recombination at breakpoint hotspots appears to be at the root of seven of the nine deletions characterized in the study, but it does not appear to tell the whole story. First, there are sequences adjacent to the deletion breakpoints that have the same level of similarity—and even longer segments of perfect identity—as those involved in the deletions, yet they do not seem to undergo homologous recombination. Second, there are two deletion cases that cannot be explained by homologous recombination. The authors propose that factors in addition to homology play a role in the deletion mechanism.

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On the Twin Risk in Autism, *by Hallmayer et al.* **(*p. 941*)**

Increased Rate of Twins among Affected Sib Pairs, *by Visscher* **(*p. 995*)**

In two recent papers, Greenberg et al. (Am J Hum Genet 69:1062–1067) and Betancur et al. (Am J Hum Genet 70:1381–1383) found evidence that twinning may be a risk factor contributing to autism. In these studies, an excess of MZ twins (and DZ twins in the Greenberg et al. study) was found in samples of affected sib pairs. In this issue of the *Journal*, a letter to the editor by Peter Visscher suggests that an excess of twin pairs, particularly MZ twins, would be expected in a sample of affected sib pairs if genetic factors contribute to the development of the disorder of interest. Dr. Visscher suggests that a population-based study may be a better way to examine this issue, and Hodge et al., the authors of the reply to this letter, concur. Lucky for us, Hallmayer et al. performed a population-based study of autism in western Australia. Their results do not suggest an excess of autism among twins. Hallmayer et al. reason that the high proportion of autistic twins found among affected sib pairs is due to the high concordance rates in MZ twins versus siblings and to fact that there is a higher proportion of twins among families with two or more children. Two other recent studies also present data on the rates of twinning in autism. Hultman et al. and Croen et al. (see citations in Hallmayer et al.) reported population-based studies in Sweden and California, respectively. Hultman et al. did not find a difference in twinning rates between a sample of individuals with autism and the general population. Croen et al. did find a slight increase in twinning in their autism sample, although a considerably smaller increase than those seen by Greenberg et al. and Betancur et al.

RNASEL *Mutation and Prostate Cancer in Ashkenazi Jews,* *by Rennert et al.* **(*p. 981*)**

Recent studies have reported evidence that variation in *RnaseL* is associated with familial prostate cancer (see Carpten et al. and Rökman et al. references in Rennert et al., as well as Wang et al. [Am J Hum Genet 71: 116–123]). Rennert et al. examined this gene in the Ashkenazi Jewish population and propose that they have identified a founder mutation. They first identified the novel 4-bp deletion, 471delAAAG, in an affected sib pair. Tissue samples were available from one of the brothers in this sib pair, and these were used to show loss of heterozygosity for *RNaseL* in tumor tissue but not in tissue with benign prostatic hyperplasia. The 471delAAAG mutation was found at slightly, but not significantly, increased rates in unselected Ashkenazi prostate cancer patients versus a group of Ashkenazi women that served as a population control. Additional population-based studies are required to determine the role of 471delAAAG in risk of prostate cancer. However, it is interesting that the 471delAAAG mutation is also found in LNCaP cells, a commonly used human prostate cancer cell line.

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