This Month in the *Journal*

Molecular evolution, the topic for this issue's series of reviews, concerns the changes in DNA sequence that drive, or at least accompany, phenotypic changes that occur as species diverge. Olson (p. 18) argues that many adaptive mutations involve not the fine tuning of gene regulation but simply the loss of gene function. Liao (p. 24) discusses the tendency of recently duplicated genes to constrain each other's divergence. This phenomenon leads to the concerted evolution of gene families, which restricts the genome's ability to use duplicated genes in new ways. Concerted evolution seems to occur largely through gene conversion, and Schimenti (p. 40) reviews the mechanism and regulation of this and other forms of homologous recombination. Goodman (p. 31) discusses the place of our species among the other primates. Judging by genetic and physiological criteria, he indicates that humans and chimpanzees should be considered to belong to a single genus.

***PWS Caused by Disruption of* SNRPN,** *by Kuslich et al.* (*p. 70*)

Kuslich and colleagues describe a boy with Prader-Willi syndrome (PWS), a developmental disorder that leads to intellectual impairment, obesity, and characteristic behavioral patterns. PWS occurs when *SNRPN* and other linked genes, which are normally expressed only from paternal 15q, fail to be expressed from either allele. The defect in the present case is unusual in that it results from a reciprocal translocation, which disrupts *SNRPN* so that only the first two exons of the gene are expressed. Because at least one other expressed sequence is silenced by this translocation, it remains uncertain whether loss of *SNRPN* is sufficient for PWS. Other reports of 15q translocations have implicated the *IPW* gene in PWS; Kuslich et al. suggest that both genes must be expressed to permit normal development.

Peroxisomal Bifunctional Protein Deficiency, *by van Grunsven et al.* (*p. 99*)

Peroxisomal diseases are often diagnosed by testing a patient's cells for complementation with a panel of previously characterized somatic cells harboring known defects in peroxisome biosynthesis or function. This method bypasses a large number of metabolic and cellular studies, but it relies on the accuracy of the initial studies. van Grunsven and colleagues now show that a metabolic deficiency previously ascribed to the peroxisomal L-bifunctional protein in fact arises from a defect in a different enzyme, the D-bifunctional protein. The two proteins both owe their names to the fact that they catalyze two sequential reactions in fatty-acid oxidation. However, these two enzymes differ in their substrate specificity and in the structure of the reaction intermediates that they produce. van Grunsven et al., noting that isolated L-bifunctional protein deficiency could not explain the metabolic properties of cells from this group of patients, have now reexamined the cell lines that originally defined the complementation group. In each case, the gene for D-bifunctional protein carried one or two identifiable mutations, and the sequence of the L-bifunctional protein was free of probable disease alleles.

Leaky Translation and Rh_{null} Syndrome, *by Huang et al.* (*p. 108*)

Rh-positive or -negative status is defined by the presence or absence of the RHD gene product in a multiprotein complex found on the erythrocyte surface. However, this Rh-complex can take different forms, so lack of RhD expression need not indicate that the complex is absent. Some forms of the complex, found in Rh-positive and in Rh-negative people, contain the structurally similar RhCE protein, instead of RhD. The two genes, *RHD* and *RHCE,* are highly homologous and tightly linked, and their two products constitute the Rh30 protein family. Isolated loss of RhD is common and benign, but the complete absence of Rh30 surface expression leads to fragile erythrocytes and chronic hemolytic anemia. This Rh_{null} phenotype may arise when homozygous deletions that affect *RHCE* occur in an individual who does not express RhD. A more common cause involves defects in the Rh-associated glycoprotein gene (*RHAG*), whose product, Rh50, copurifies with each of the Rh30 proteins. Rh50 appears to be required for surface expression of the complex, so mutations in *RHAG* can cause disease irrespective of *RHD* and *RHCE* expression. Huang et al. have identified a novel mutation in the translational initiation codon of RHAG in an Rh_{null} woman with wild-type *RHD* and *RHCE* alleles. mRNA containing this lesion is processed normally and can be translated in vitro from internal methionine codons. The authors suggest that the ability of ribosomes to bypass the mutation may explain some leakiness in such cases.

Dissecting Phenotypes in Williams Syndrome, *by Tassabehji et al.* (*p. 118*)

Tassabehji et al. have studied the cognitive phenotype associated with Williams syndrome (WS), a contiguous

0002-9297/99/6401-0001$02.00

gene–deletion syndrome that affects 7q11. Haploinsufficiency for one or more of the genes in this region causes aortic stenosis, a result of insufficient elastin (ELN) expression. Affected people also exhibit a specific defect in visuospatial cognition, the ability to recall spatial relations within an image and to manipulate them in the imagination. This aspect of the phenotype has been associated with deletion of *LIMK,* which encodes a kinase restricted to the central nervous system. However, Tassabehji and colleagues show that small deletions that affect *ELN* and *LIMK* do not cause the WS cognitive profile in carriers, contrary to earlier reports. This finding might be reconciled with the earlier reports if haploinsufficiency for *LIMK* were to cause the cognitive phenotype with incomplete penetrance. However, Tassabehji et al. stress that the lack of visuospatial reasoning is among the most consistent of the WS characteristics.

Chromosome 6p QTL Involved in Dyslexia, *by Fisher et al.* (*p. 146*)*; and* ***QTL for Reading on 6p,*** *by Gáyan et al.* (*p. 157*)

Two reports in this issue confirm that a quantitative-trait locus for reading ability maps to 6p21. Earlier work had linked several of the parameters used to measure dyslexia to this locus. Although they applied different psychological tests, both groups analyzed phonological abilities, such as the facility with isolated speech sounds that is needed to speak in Pig Latin, as well as orthographic skills, such as the ability to recognize words with irregular spelling. Fisher et al. (p. 146) studied British sib pairs that included at least one dyslexic child, whereas Gáyan et al. (p. 157) ascertained their subjects and controls through a search for twins attending Colorado schools. Both groups confirm that phonological and orthographic deficits map to this region. Although many of the measures used by either group showed strong or suggestive linkage over several centimorgans, the point of maximum linkage varied somewhat between tests. To achieve still finer mapping as a prelude to cloning, it may be necessary to focus on just one or a few phenotypic measurements.

Linkage of Bipolar Disorder to 21p22, *by Aita et al.* (*p. 210*)

Aita and colleagues also provide welcome confirmation of linkage to a psychological trait. This same group had previously identified a putative locus for bipolar disease at 21q22, on the basis of data from a single large family. Now they report that this linkage persists in a set of 40 American and Israeli families. The authors focused on concordant sib pairs, whom they categorized as affected according to any of three diagnostic models. When analyzed under the least restrictive of these models, the location of the peak LOD score agrees with earlier findings. The gene's location within the intensively studied Down syndrome critical interval may hasten the discovery of a susceptibility locus in this region.

Rapid Clearance of Circulating Fetal DNA, *by Lo et al.* (*p. 218*)

Fetal cells in maternal circulation could supply useful information for prenatal counseling, obviating the need for invasive sampling methods. However, as Lo et al. point out, this approach is limited by the fact that such cells can persist for years after a first pregnancy and can confuse analysis in later pregnancies. Free fetal DNA in maternal plasma could provide an attractive alternative to whole-cell analyses if it is cleared more efficiently. Lo et al. report here that, of 12 women carrying male fetuses, all had quantifiable amounts of a Y chromosome–specific marker circulating in their plasma when they were tested before delivery. This marker was undetectable afterward, even when the women were tested on the day after delivery.

Inbreeding and Fertility, *by Ober et al.* (*p. 225*)

Ober and colleagues have followed the fertility of a South Dakota Hutterite population for 15 years, and they now report that the degree of inbreeding affects the rate at which women in this traditional and reproductively isolated group become pregnant. Neither paternal inbreeding coefficients nor the degree of consanguinity between husband and wife had a significant effect on couples' reproductive history, but high maternal inbreeding coefficients are associated with longer times between pregnancies. However, highly inbred women were no more likely than others women in the community to undergo spontaneous abortions, so the effect of inbreeding most likely occurs at or before implantation. Surprisingly, these women's relative difficulty in conceiving did not, on the whole, cause them to have fewer children but caused them only to take longer to reach their families' ultimate size. Ober et al. suggest that this "reproductive compensation" is possible only because, in recent years, the overall number of children per family has dropped from >10, the likely biological maximum for this population, to ~8.

JOHN ASHKENAS
Editorial Fellow