This Month in the *Journal*

The interphase nucleus of a human cell is anything but a homogeneous compartment, but the principles by which chromosomes and other intranuclear bodies are organized within this space remain uncertain. Even the apparently simple question of whether the nucleus possesses a fibrous skeleton has been debated fiercely for decades. Here we present four reviews on the structure and composition of the nucleus. Paddy (p. 305) discusses work on the human and *Drosophila* Tpr protein and presents an alternative formulation of the nuclear-matrix hypothesis, the extrachromosomal-channel model. He argues that this model accommodates both the available data on the ultrastructure of the nucleus and the biochemical features of Tpr, which localizes to channels that connect the nuclear pore and the interior of the nucleus. Dasso and Pu (p. 311) review the regulation of transport between the nucleus and the cytoplasm by the small GTP-binding protein Ran and its soluble or nuclear pore–associated partners. This regulation is dynamic in that it is coordinated with the status of the cell in the cell cycle, and it appears to be altered by heat shock and circumvented by the HIV virus. Likewise, as Hodges et al. (p. 297) show, PML bodies, a class of intranuclear organelle, reorganize and change in size and number during the cell cycle and in response to viral infection, and these events may be coordinated with control of transport through nuclear pores. PML bodies house several classes of oncogenic fusion proteins, and Hodges et al. consider the evidence that mislocalization of PML-body components in cells that carry common chromosomal translocations is a key step in human leukemia. Finally, Matera and Frey (p. 317) discuss the relationship between two classes of intranuclear structures: coiled bodies, where components of small nuclear ribonucleoprotein particles (snRNPs) accumulate, and "gems," where the product of the *Survival of Motor Neuron 1* gene is found. The close association—and possible identity—between these structures may implicate snRNP biogenesis in the development of spinal muscle atrophy.

Null Mutations in* cblG *Variants, *by Wilson et al. (p. 409)*

Defects in the biochemical pathway that generates methionine from homocysteine may arise from mutations in several genes, and these different etiologies can be distinguished by cell-fusion experiments. Several such mutations, particularly those in complementation groups *cblG* and *cblE,* are similar in their clinical presentation; both classes of mutations lead to developmental delay, seizures, and abnormal hematopoiesis. Patients in the *cblG* group carry defects in *MTR,* the structural gene for methionine synthase (MS). Typically, such individuals show some residual MS activity, but in the "cblG variant" phenotype, MS activity is undetectable, and the methylcobalamine cofactor fails to associate with MS protein. Here, Wilson and coworkers show in two families that the cblG variant arises from compound heterozygosity for null mutations in *MTR*. In all affected individuals, expression of the gene is drastically reduced, but, by amplifying and sequencing the trace amount of residual mutant mRNAs, Wilson et al. show that each of the four alleles introduces premature breaks in the *MTR* reading frame, apparently leading to efficient nonsense-mediated decay.

Molecular Epidemiology of the MELAS Mutation, *by Majamaa et al. (p. 447)*

Because of their many phenocopies and their idiosyncratic progression in different people and different tissues, mitochondrial diseases present a challenge for population studies. With the identification of specific mtDNA disease alleles, however, it has become practical to address the epidemiology of these disorders at the molecular level. Here, Majamaa and coworkers report the frequency of one common point mutation that is known to cause mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS). Through state-held medical records, they ascertained a substantial majority of the adults living in one Finnish province whose histories included any of the symptoms of MELAS, and they used reverse transcription–PCR to find mutation carriers. The mutation was associated with at least four different mitochondrial haplogroups, so it is likely to have arisen several times independently. If the prevalence that they observe in this population is representative, the MELAS mutation may be a significant factor in several disorders, including ophthalmoplegia and hypertrophic cardiomyopathy.

Nucleotide Substitution Rates, *by Krawczak et al. (p. 474)*

The presence of a cytosine in a CpG dinucleotide dramatically increases its likelihood of undergoing a transition, but no other features of DNA sequence are known to promote specific classes of nucleotide substitution. Krawczak et al. have scanned a large human-mutation database, looking for regularities among the sequences

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surrounding the sites of different classes of mutations. Because the database largely catalogs lesions that lead to disease, the authors attempt to compensate for biases by modeling the likelihood of clinical detection of each mutation. Analysis of their corrected data set confirms the high mutability of CpG sequences and suggests that regions with high thermodynamic stability (i.e., those with a high predicted temperature of strand separation) are relatively prone to substitutions, possibly because stable duplexes are less accessible to DNA proofreading enzymes.

Genetic Control in Human Malaria, *by Rihet et al.* (*p. 498*)

Rihet and colleagues have reported a non-Mendelian pattern of segregation for the level of parasitemia in a western African population that is exposed to endemic *Plasmodium falciparum*. Following up on this analysis, they now implicate in the control of this quantitative trait a distal 5q region that is rich in genes related to immune function. Rihet et al. collected blood samples, at monthly intervals, from members of 34 families in Burkina Faso. During a period of 21 months, they report, individual levels of parasite density remain consistent, and markers in the 5q31-q33 region can be used to predict levels that are concordant or discordant between sibs. Rihet et al. conclude from their sib-pair analyses that nearly half of the interindividual variation in blood-infection levels is under the control of one or more genes in this region. Other loci that might interact with genes in the 5q candidate region may be identified through the genetics of the similar quantitative trait that segregates in crosses between inbred mouse strains.

MNGIE Syndrome Maps to 22q13.32-qter, *by Hirano et al.* (*p. 526*)

Among the numerous familial mitochondrial myopathies, three are unusual in that they are associated with nuclear genes and in that they affect oxidative phosphorylation only indirectly, by destabilizing the mitochondrial genome. Linkage data are available for two of these mtDNA deletion syndromes—progressive external ophthalmoplegia (PEO) and Wolfram syndrome. Now, Hirano and coworkers show that the third, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), maps to a distal locus on 22q. MNGIE is a rare recessive disease whose symptoms outside muscle tissue partially overlap with those of the autosomal dominant PEO, but each these multisystem disorders affects a unique set of tissues. This specificity may not be explained until all of the relevant genes are identified.

FCH Families and Coronary Artery Disease, *by Allayee et al.* (*p. 577*)

Familial combined hyperlipidemia (FCH), defined by elevated levels of both LDL and triglycerides in the blood, is associated with high risk of coronary artery disease. Another feature that is common in the blood of FCH individuals—but that usually is regarded as an independent risk factor for heart disease—is the presence of relatively small, dense LDL particles. Allayee and colleagues have studied the LDL buoyant-density profile in FCH families. They report that three of four loci previously linked to control of LDL particle size in the general population appear to be important in these families as well. The authors discuss a number of linked candidate genes, including those for apolipoproteins, superoxide dismutase, and several enzymes that act in cholesterol metabolism, all of which could alter the synthesis or processing of LDL particles.

Amplification to Gene in Thyroid Cancer, *by Chen et al.* (*p. 625*)

Here, Chen et al. demonstrate the power of high-resolution FISH to find small aneuploid regions in tumor cells, an approach that has allowed them to identify protein kinase C-ϵ (PKCϵ) as a novel candidate oncoprotein. Using comparative genomic hybridization across the entire genome, they identified several amplified or deleted regions common to independent thyroid adenomas or carcinomas, but they focused on one locus, 2p21, which was amplified in one quarter of these tumors and was present in a double minute chromosome in a thyroid cell line. By hybridizing bacterial artificial chromosomes (BACs) from chromosome 2 to the various cell and tissue samples, Chen et al. narrowed a critical region to <6 Mb. From this, they sequenced a single 67-kb BAC that contains part of the gene for PKCϵ and showed that this gene is rearranged and amplified. The authors argue that their approach should succeed wherever a sufficiently high-density–ordered BAC map is available to the chromosome of interest.

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