mtDNA Deletions in Aged Human Muscle, by Bua et al. (*p. 469*)

As people age, they lose lean muscle mass, primarily through muscle-fiber atrophy and a decrease in the number of muscle fibers. This loss, or sarcopenia, is usually accompanied by abnormalities in the electron-transport system (ETS). mtDNA deletions also accumulate with age, and previous work has demonstrated that cells with high levels of mtDNA deletions have abnormal ETS activity. It remained uncertain whether it is the abundance of mtDNA deletions that eventually leads to the loss of muscle mass. This cannot be determined by examining the whole tissue, because the accumulation of mtDNA-deletion species and ETS abnormalities occur in a mosaic fashion throughout the muscle. Here, Bua et al. closely examined the mtDNA and the ETS function in serial sections along the length of muscle fibers from individuals of various ages. They show that, with age, the number and length of regions with ETS abnormalities increase. Within these regions, the intracellular level of mtDNA with deletions accounted for >90% of the total mtDNA. Fibers with normal ETS activity had only wild-type mtDNA. Various mtDNA deletions were identified, but each region of ETS dysfunction was clonal, harboring the same deletion. Along the borders of these regions, there were transitional areas where the levels of the mtDNA with deletions declined and ETS activity was normal. This suggests that it is the accumulation of the mtDNA with deletions that causes the ETS abnormalities and the eventual fiber loss.

Fast Computing of Association Significance, by Kimmel and Shamir (*p. 481*)

A common problem faced by all researchers doing association studies is how to properly correct for multiple testing. As technology makes it ever more possible to type thousands of markers in thousands of samples, new methodology is necessary to properly measure the observed effects. It is known that a Bonferroni correction is too conservative, and this overcorrection becomes even more pronounced as the number of SNPs increases. Permutation tests are traditionally used to measure the exact amount of significance of an association, but permutations require a large number of operations, and the time for calculations can be restrictive when evaluating a large number of markers. This time burden is also limiting when the tests are used to measure the significance of the interactions among multiple loci. Kimmel and Shamir developed a new method, Rapid Association Test (RAT), that significantly decreases the time needed to evaluate significance by incorporating importance sampling and linkage-disequilibrium decay. This method has a great advantage over regular permutation tests when a *P* value is low and several permutations are necessary to evaluate an association. When RAT was compared with permutation tests in simulations and on HapMap data, RAT was 3–5 orders of magnitude faster.

X-Inactivation Patterns, by Amos-Landgraf et al. (*p. 493*)

During the development of female mammals, one X chromosome is inactivated so that, similar to the situation in males, only one copy of most X-chromosome genes is expressed. In females with two normal copies of X, it is thought that inactivation takes place randomly, so that there is an approximately equal number of cells expressing each of the X chromosomes. This ratio can be skewed in special cases, especially when the female is a carrier of an X-chromosome disorder. It is thought that then, during development, the cells in which the normal X chromosome remains active have a growth advantage over those in which the abnormal X is selected. For skewing to be used as a marker for carrier females, it is important to have a comprehensive understanding of the variability of skewing present in females with a normal phenotype. Other groups have made an effort to establish a baseline measurement of skewing, but good reproducibility of the assays has not always been obtained. Here, to achieve a high level of replication and to evaluate the X-inactivation ratio of 1,005 unaffected females, Amos-Landgraf et al. optimized their assay parameters. Overall, <8% of the studied females had a skewed ratio of >80:20 or <20:80. This framework allows the authors to propose that, if a ratio of >90:10 or >95:5 is observed during screening, it is likely that an X-chromosome defect is present.

Meiosis, Recombination, and the t(11;22), by Ashley et al. (*p. 524*)

The translocation t(11;22)(q23;q11) is rare but recurrent in germ cells. The rearrangement has been highly observed during male meiosis, but it is unclear why these two chromosomes are involved more often than other chromosomes. The presence of lengths of palindromic AT-rich sequence at the breakpoints on each chromosome has suggested that the repair and recombination following a double-stranded break (DSB) of a DNA hairpin are involved. But, because such DSB repair occurs throughout the genome, this does not explain why chromosomes 11 and 22 specifically are recurrently involved. It is possible that the bands involved in the rearrangement are each recombination hotspots. In addition, previous work has

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demonstrated that the organization of the chromosomes during meiosis is not random. Using FISH and immunocytochemistry, Ashley et al. marked the two chromosomes during meiosis, as well as a protein involved in recombination. They discovered that the breakpoints on chromosomes 11 and 22 are not hotspots but that their close proximity to each other during meiosis is most likely a key factor in their recurrent rearrangement with each other.

CEP290 Mutations Are a Frequent Cause of LCA, by den Hollander et al. (p. 556)

Eight genes have been associated with the genetically heterogeneous Leber congenital amaurosis (LCA), a type of recessive severe retinal dystrophy. den Hollander et al. describe a French Canadian LCA-affected family in which a genomewide linkage scan suggested a new locus on 12q21-q22. The affected members of the families are found to be homozygous for a splice-site mutation in the gene *CEP290.* This mutation leads to the transcription of an abnormal truncated transcript, along with residual levels of the wild-type (WT) transcript. Screening of 76 unrelated patients with LCA from various geographical locations identified 16 other individuals with mutations in *CEP290,* all of whom had at least one copy of the splice-site mutation. The predicted frequency of *CEP290* mutations in LCA suggests that dysfunctional *CEP290* is one of the most common causes of the disease. Homozygous mutations in *CEP290* have also been linked to Joubert syndrome, a neurological disorder often associated with renal disease and retinal dystrophy. It is suggested that the low levels of WT transcript produced by the splice-site variant are enough to ensure proper neurological and kidney function in patients with LCA.

This Month on the Cover

The image on the cover is the chemical structure of phenylalanine, the amino acid that cannot be metabolized by patients with phenylketonuria (PKU). In 1934, Asbjörn Følling first reported patients who had elevated levels of phenylpyruvic acid in their urine and demonstrated an associated mental retardation (Zeitschrift für Physiologische Chemie 227:169–176). It was later determined that PKU was caused by a deficiency of the enzyme phenylalanine hydroxylase, which is needed for proper phenylalanine metabolism (Nature 306:151–155). It is the build-up of the amino acid that causes the PKU phenotype and, as first demonstrated by Bickel et al. in 1953, treatment with a diet low in phenylalanine can alleviate PKU symptoms (Lancet 2:812–813). Today, cases are detected through newborn screening, and, by adhering to restricted diets, affected individuals can develop normally. PKU is a landmark example of a genetic disease that can be effectively diagnosed and treated.

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