Beyond huntingtin in Huntington disease

More than a decade has passed since the identification of CAG triplet expansions in huntingtin as the cause of Huntington disease. Members of the US-Venezuela Collaborative Research Project now report some of the strongest evidence yet for the existence of genetic and environmental modifiers that influence the age of onset of this fatal neurological illness (*Proc. Natl. Acad. Sci. USA* 101, 3498–3503; 2004). Nancy Wexler and colleagues have been studying kindreds in the Lake Maracaibo region of Venezuela since 1979, amassing information on more than 18,000 individuals. The authors confirm a negative correlation between the length of the expansion and age of onset; for those with repeat lengths between 40 and 50, however, the size of the expansion accounts for less than one-half of the variance in age of onset. As much as 84% of this 'residual' variance in age of onset is familial and probably due to modifier genes and shared environmental influences. Noting that the genetic component of this residual effect on age of onset is comparable to that seen for other complex traits, the authors suggest that linkage mapping to identify modifiers stands a good chance of success. ***AP***

Human geography of the African diaspora

During the 400 years ending in the nineteenth century, the Atlantic slave trade resulted in the forced displacement of approximately 13 million people from Africa, mostly to the Americas, with about 11 million of the captive people surviving the voyages. Salas *et al.* (*Am. J. Hum. Genet.* **74**, 454–465; 2004) have made the first attempt to trace the maternal ancestry of Americans to particular regions of Africa by comparing the mitochondrial (mt) HVS-1 sequence motifs of 481 American individuals of African ancestry with those of over 2,000 geographically localized Africans. The frequency distributions of mtDNA haplogroups they found were consistent with historians' data that people enslaved in North and Central America came from west and west-central Africa, and those in Brazil from west-central Africa. Attempts to trace the ancestry of individuals to smaller regions is problematic because, although regions are well described by the haplogroup frequency profiles, the correspondence of individual mtDNA variants with geographical locations is not straightforward. Further obstacles to biological anthropology of the historical African diaspora are that all the regions of Africa have not been studied, and that the dispersal of Bantu peoples in recent prehistoric times distributed a small set of mtDNA types throughout sub-Saharan Africa. *MA*

Dynamic view of transcription

Activation of gene transcription in eukaryotes requires substantial changes in chromatin organization. Using an inducible system, Susan Janicki and colleagues (*Cell* **116**, 683–698; 2004) provide new mechanistic insights into the dynamic nature of this process. The authors applied fluorescence-labeling techniques in living cells to monitor changes in DNA, RNA and protein in real time. After stimulation, the authors observed an immediate and steady increase in RNA levels that coincided with a progressive shift in chromatin structure at the activated locus. This shift was marked by changes in both chromatin condensation and histone composition. In particular, the locus underwent a steady depletion of the heterochromatin protein HP1α and a progressive deposition of the histone H3 variant H3.3. Notably, methylation of histone H3 at lysine 9 has previously been associated with the recruitment of HP1α to silent chromatin, and no enzymes have been discovered that can reverse this modification. Together with results from other studies, these findings suggest that replacement of H3 by H3.3 might be an alternate mechanism for establishing or maintaining active chromatin states. *KV*

Research Notes written by Myles Axton, Alan Packer, Michael Stebbins and Kyle Vogan

Hold your fire

Efforts to analyze the S-phase response to DNA damage in human cells have been limited by available methods. Catherine Merrick and colleagues now describe a DNA fiber labeling approach that can quantify rates of replication origin firing, and rates of fork movement and stalling, in individual cells (*J. Biol. Chem.* advance online publication, 27 February 2004; doi:10.1074/jbc.M400022200). The method involves pulse-labeling newly replicated DNA with halogenated nucleotides, lysing the cells on a slide and 'tipping' the slide so that the DNA is spread out in single fibers. Immunodetection of the modified nucleotides then allows one to follow replication fork dynamics depending on the length of the pulse. Merrick *et al.* find that the intra-S-phase checkpoint response in HeLa cells is essentially the same as that previously reported for yeast cells. Specifically, origin firing is inhibited rapidly after treatment with methyl methane sulfonate, hydroxyurea or ionizing radiation. Methyl methane sulfonate and hydroxyurea also slow fork movement and induce stalling, although ionizing radiation does not. The authors suggest that this single-cell method will have particular value in determining the checkpoint responses of tumor cells to different chemotherapeutic agents. *AP*

A universal microarray

The cost of producing a new microarray platform for every species being analyzed is daunting to say the least. But there is a particular need for such experimental tools among those interested in comparative functional genomics. So far, universal microarray technologies have been either prohibitively costly or plagued with technical difficulties. Now, Mathew Roth and colleagues describe a new universal microarray that will allow analysis of any genome without having to print a new array (*Nat. Biotechnol.* 22, 418–426; 2004).They built a microarray platform using 4,096 DNA hexamers and developed an accompanying molecular biological process for transcriptome treatment. The process starts with conversion of expressed RNA into cDNA followed by digestion with endonucleases to generate equal length DNA fragments. The fragments are then amplified and ligated to labeled detector and the array, creating 14-bp, transcript-derived sequence tags. The authors validated their system by looking at the yeast galactose response pathway. They estimate that approximately one-third of the primary signals were in fact unmapped, 10% of which were caused by mismatch during the ligation process. Nevertheless, further tweaking of hexamer-based microarray platforms could substantially improve the ease of expression analysis. ***MS***