Research Highlights

Social imprinting

Theoretically, imprinted genes can affect social behaviour — especially if the gene might confer a better or worse chance of reproductive success. The first example of such a gene has now been reported by Garfield and colleagues. The gene is *Grb10*, encoding an adaptor protein which associates with several receptor tyrosine kinases. The brain selectively expresses the paternal allele and, on disruption of this allele, mice became distinctly more dominant. The maternal allele is expressed by entirely different tissues and its disruption has no effect on behaviour.

Garfield, A.S. *et al.* (2011), 'Distinct physiological and behavioural functions for parental alleles of imprinted *Grb10*', *Nature* Vol. 469, pp. 534–538.

Delicious genomes

The genomes of *Theobroma cacao* (chocolate) and *Fragaria vesca* (strawberry) have been reported this month. These will undoubtedly provide us with valuable information concerning flavour genes, as well as genes relating to products of nutritional value. *F. vesca* is also of value as an experimental model system, as it is easily transformable, hardy and has a fast generation time. *T. cacao*, unlike *F. vesca*, is far from hardy and needs some help. As the primary source of high-quality chocolate, this particular cacao variety is of great economic (and gastronomic) interest. Much of the crop is lost to pests and other natural hardships, however, and hardier varieties of cacao do not produce chocolate of the same quality. No word yet on a cacao/vesca hybrid.

Argout, X. *et al.* (2011), 'The genome of *Theobroma cacao*', *Nat. Genet.* Vol. 43, pp. 101–109.

Shulaev, V. *et al.* (2011), 'The genome of woodland strawberry (*Fragaria vesca*)', *Nat. Genet.* Vol. 43, pp. 109–116.

An aspirin a day

Previous work has suggested that daily low-dose aspirin might decrease the risk of certain cancers, such as colorectal cancer and cancers of the gastrointestinal tract. As the trials have become more rigorous, however, the actual benefit has appeared to decrease. A recent meta-analysis of trials addressing this issue has finally generated strong evidence for decreased risk. Risk was decreased by about 20 per cent for many common cancers and for widely different populations. The surprise was the length of time necessary for this effect to manifest. A minimum of five years of daily aspirin seems to be required, with some cancers showing decreased risk only after 20 years.

Rothwell, P.M. *et al.* (2011), 'Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials', *Lancet* Vol. 377, pp. 31–41.

Silence of the genes

Fragile X syndrome is associated with the hypermethylation of the (aptly named) fragile X mental retardation 1 (*FMR1*) gene promoter. Hypermethylation induces silencing of *FMR1*, with a number of downstream consequences, including upregulation of metabotropic glutamate receptor 5 (mGluR5) signalling. While testing the ability of an mGluR5 inhibitor to treat patients suffering from fragile X syndrome, Jacquemont and colleagues thought to correlate the clinical efficacy (or lack thereof) with the extent of promoter methylation. They found a strong correlation between efficacy and full methylation of the promoter. Hopefully, this will be replicated in a larger and longer trial.

Jacquemont, S. *et al.* (2011), 'Epigenetic modification of the *FMR1* gene in fragile X syndrome is associated with differential response to the

mGluR5 antagonist AFQ056', *Sci. Transl. Med.* Vol. 3, p. 64ra1.

Chemoproteomics to the rescue

Histone deacetylase (HDAC) inhibitors are a tantalising drug class with potential applications to cancer, autoimmunity and neurodegeneration. The problem lies in obtaining specificity. These proteins lie at the cores of megadalton complexes, which are to some extent cell specific and involve a combinatorial assembly of components. Inhibitors, by targeting individual proteins, can affect multiple complexes. Bantscheff and colleagues have employed a combination of affinity capture of these complexes coupled with quantitative mass spectrometry (chemoproteomic analysis) to create an assay capable of screening for complex specific inhibitors. Using this methodology, they analysed several existing HDAC inhibitors and demonstrated both off-target effects and surprising specificities.

Bantscheff, M. *et al.* (2011), 'Chemoproteomics profiling of HDAC inhibitors reveals selective targeting of HDAC complexes', *Nat. Biotechnol.* Vol. 29, pp. 255–265.

Disagreeable data

Deletions, duplications and inversions of genomic sequence are becoming targets of inquiry because of the role they may play in the aetiology of complex diseases. The ability to identify and enumerate these sequences is obviously a necessary first step towards understanding that role. As with most things genomic, we 'see' these structures by employing software packages. Recently, Zhang and coworkers undertook the job of evaluating four of the major copy number variation (CNV) detection suites: Birdsuite, Partek, HelixTree and PennCNV-Affy. Their conclusion was that there was often great disagreement between the various programs. Anyone using CNV analysis to understand their favourite disease should look closely at this evaluative study.

Zhang, D. *et al.* (2011), 'Accuracy of CNV detection from GWAS Ddta', *PLoS One* Vol. 6, p. e14511.

Regional DNA methylation

The means by which DNA methylation regulates gene expression within mammalian cells is still poorly understood. The methylation of cytosines within the promoter has long been known to correlate with gene silencing; however, less is known about patterns of methylation elsewhere. Brenet *et al.* developed a means to enrich for and identify methylated sequences, and have used this to perform a whole-genome scan. Interestingly, they found that exonic sequences were highly enriched within the methylated fraction — more so than would be predicted. While there was some correlation between promoter methylation and gene silencing, as has been previously described, a far better correlation was seen between silencing and methylation within the first exon. Other intragenic regions showed interesting patterns of methylation but this did not correlate with transcription.

Brenet, F. *et al.* (2011), 'DNA methylation of the first exon is tightly linked to transcriptional silencing', *PLoS One* Vol. 6, p. e14524.

FOXA hunting

Breast cancers kill many women — in part, because their tumour cells become resistant to chemotherapies. As oestrogen receptor (ER) activity is a critical component of these cancers, understanding resistance will most likely require an understanding of the molecular basis for ER activity. Progress in this area was recently reported by Hurtado and colleagues. They found that the Forkhead transcription factor; FOXA1 (also called HNF3α) is a key component mediating interactions between ER and chromatin. Using Chip-Seq, they demonstrated that inhibition of *FOXA1* expression markedly reduced ER binding at virtually all genomic locations. Even in tamoxifen-resistant cells, ER binding was dependent on the FOXA1.

This bodes well for those interested in developing new therapeutics to combat this deadly disease.

Hurtado, A. *et al.* (2011), 'FOXA1 is a key determinant of estrogen receptor function and endocrine response', *Nat. Genet.* Vol. 43, pp. 27–33.

DeletionsDeleInsertionstions

The 1000 Genomes Project continues to bear fruit. Mills and co-workers have used this terabyte dataset to look for copy number variants. This combination of duplications, deletions and insertions represents a greater fraction of the genome than do single nucleotide polymorphisms and yet comparatively little is known about them. Their effect on certain heritable diseases, such as schizophrenia, is incontrovertible. The current study begins to give structure — and, eventually, meaning — to the universe of human genomic structural variation.

Mills, R.E. *et al.* (2011), 'Mapping copy number variation by population-scale genome sequencing', *Nature* Vol. 470, pp. 59–65.

New loci for heart disease

Coronary artery disease (CAD) is heritable but complex and thus difficult to tease apart genetically. Reilly and colleagues attacked this problem by creating stringent requirements for CAD to decrease heterogeneity in their population. They performed not one, but two genome-wide association studies, focusing first on patients with CAD, as compared with patients without, and then on patients with CAD, as compared with patients with CAD plus myocardial infarction (MI). For CAD, they identified ADAMTS7, a metalloproteinase which affects vascular smooth muscle migration and thus neointimal thickening. Not surprisingly, the ABO locus associated with MI. The identification of ADAMTS7, in particular, may provide us with an interesting new therapeutic target.

Reilly, M.P. *et al.* (2011), 'Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: Two genome-wide association studies', *Lancet* Vol. 377, pp. 383–392.

The disease allele debate rages on

Are common diseases with genetic components driven by common disease alleles or rare ones? About a year ago, the laboratory of David Goldstein contributed to the missing heritability question by proposing that *rare* gene variants associate with common alleles to create 'synthetic associations' and that these might provide a genetic basis for common diseases. Supporters of the other camp (ie common diseases are driven by *common* variants) have not been idle, however. Two critiques of the synthetic association hypothesis have now been published, along with a response from the original author. The ultimate resolution of this debate will have strong effects on the design of future association studies and so it may be worth following.

Wray, N.R. *et al.* (2011), 'Synthetic associations created by rare variants do not explain most GWAS results', *PLoS Biol.* Vol. 9, p. e1000579.

Anderson, C.A. *et al.* (2011), 'Synthetic associations are unlikely to account for many common disease genome-wide association signals', *PLoS Biol.* Vol. 9, p. e1000580.

Goldstein, D.B. (2011), 'The Importance of synthetic associations will only be resolved empirically', *PLoS Biol.* Vol. 9, p. e1001008.

Out of the Sumatran forest

Within our hominid family, the orang-utan represents a species evolutionarily as far removed from ourselves as is currently available. Once considered solitary creatures, it has become apparent that these 'men of the forest' have a complex social structure and show variability in tool use that is clearly cultural. Last month, a comparison of draft genomes from ten orang-utans from either Sumatra or Borneo was reported. It is notable that structural evolution of the orang-utan genome has proceeded far more slowly than in other great apes. Given the tremendous loss of habitat for this species, genomic

tools will provide the immediate benefit of allowing an accurate estimate of genetic diversity.

Locke, D.P. *et al.* (2011), 'Comparative and demographic analysis of orang-utan genomes', *Nature* Vol. 469, pp. 529–533.

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