CANCER GENETICS

Networks uncover new cancer susceptibility suspect

Cancer susceptibility genes such as breast cancer 1 (*BRCA1*) do not function in isolation — they are parts of networks, and deciphering how these networks operate is an important step in understanding cancer progression. A new study has constructed a network for breast cancer susceptibility using various 'omic' data sets, and identified the hyaluronan-mediated motility receptor gene (*HMMR*) as a new susceptibility locus for the disease.

The authors sought to construct a network around four genes that are known to be associated with breast cancer: *BRCA1*, *BRCA2*, ataxia telangiectasia mutated (*ATM*) and checkpoint homologue (*CHEK2*). They used published expression data from normal cells to identify 164 other genes, the expression of which correlated with all four of their reference genes. The relevance of these genes for the BRCA-related network was confirmed by the fact that their expression was in many cases upregulated in tumours from carriers of *BRCA1* mutations compared with sporadic tumours.

This list was integrated with published functional genomic data about interactions between the genes on the list. The resultant network consisted of 118 genes and proteins, with 321 direct and 545 indirect interactions. One of the most highly connected nodes in the network, and the one with the closest coexpression with *BRCA1*, was *HMMR*, which probably has a role in centrosome function.

The authors further explored the role of HMMR using a yeast two-hybrid assay, and found that HMMR interacts with several components of BRCA1 complexes. Using co-immunoprecipitation assays, the association of BRCA1 and HMMR was seen specifically as cells entered mitosis, and the authors also showed that HMMR was ubiquitylated by the BRCA1 complex and was localized to the centrosome. Knocking down either *HMMR* or *BRCA1* caused abnormal increases in centrosome number, but this effect was abolished if the expression of both genes was inhibited simultaneously.

In the light of this functional information, the authors looked for associations between SNPs in *HMMR* and breast cancer susceptibility. Typing for five SNPs in several independent populations showed that two haplotypes significantly increased susceptibility to breast cancer, and that this effect was independent of *BRCA1* or *BRCA2* status. Interestingly, expression analysis showed that one of these haplotypes was associated with an increase in *HMMR* expression whereas the other was associated with a decrease. This implies that any perturbation from a precise level is detrimental.

This study comprised several components — the construction of a network model from published data, the functional molecular characterization of a candidate component of this network, and a candidate-gene population association study to demonstrate its link with cancer susceptibility. It shows the power of network modelling to generate hypotheses for both molecular and population genetics.

Patrick Goymer

ORIGINAL RESEARCH PAPER Pujana, M. A. *et al.* Network modeling links breast cancer susceptibility and centrosome dysfunction. *Nature Genet.* 7 October 2007 (doi:10.1038/ng.2007.2)
FURTHER READING Jensen, L. J., Saric, J. & Bork, P. Literature mining for the biologist: from information retrieval to biological discovery. *Nature Rev. Genet.* **7**, 119–129 (2006) | Badano, J. L., Teslovich, T. M. & Katsanis, N. The centrosome in human genetic disease. *Nature Rev. Genet.* **6**, 194–205 (2005)

IN BRIEF

COMPLEX TRAITS

Fine mapping versus replication in whole-genome association studies.

Clarke, G. M. *et al. Am. J. Hum. Genet.* **81**, 995–1005 (2007)

The main weakness of association studies is the poor ability to confirm the association of a variant with disease in an independent study. The authors have developed a theoretical model to determine the best strategy for confirming an association: if markers show only weak linkage with disease, then the most successful route to replication involves performing a local search for both the candidate variants and nearby markers. Conversely, if the initial association was strong, then it is most fruitful to test the initially identified markers.

QUANTITATIVE GENETICS

Linking metabolic QTLs with network and *cis*-eQTLs controlling biosynthetic pathways.

Wentzell, A. M. & Rowe, H. C. *et al. PLoS Genet.* **3**, e162 (2007)

Linking the variation in gene expression on a genome-wide scale with phenotypic consequences remains a challenge. Using two well-defined metabolic pathways in *Arabidopsis thaliana*, these authors show that variation in expression of genes in these pathways can be linked to metabolite variation. This relationship is complex, and regulatory connections can feed back from metabolism to transcripts — candidate-gene analysis indicates that, for one of the pathways, it is the final enzyme that is the key regulator of transcript and metabolite levels.

EVOLUTION

Gene duplication and the adaptive evolution of a classic genetic switch.

Hittinger, C. T. & Carroll, S. B. *Nature* 11 October 2007 (doi:10.1038/nature06151)

The genetic switch that controls the yeast galactose-metabolism pathway involves two paralogues — *GAL3* and *GAL1* — that originated from a single, bifunctional ancestral gene. By precisely replacing sequences in the coding and regulatory regions of these genes, the authors provide evidence that duplication allowed the evolution of new regulatory sequences that were disfavoured when in the same gene, enabling the two duplicates to take on new functions. This work provides a rare example of experimental evidence for how gene duplications allow new gene functions to evolve.

GENOMICS

Islands of euchromatin-like sequence and expressed polymorphic sequences within the short arm of human chromosome 21.

Lyle, R. *et al. Genome Res.* 25 September 2007 (doi:10.1101/gr.6675307)

The Human Genome Project focused on euchromatin, leaving unsequenced the ~6.5% of the genome that is heterochromatic. The authors constructed BAC clones of a region of the heterochromatic short arm of the acrocentric chromosome 21. Sequencing this region uncovered several potential genes, and a surprising amount of copy-number and sequence variation. Expression profiling showed that 10 of the 26 potential genes in this region are expressed in various tissues, although it is not known whether they are genes or pseudogenes.