Editorial

Epidemiological data have shown that chronic alcohol consumption increases the risk for cancer of the organs and tissues of the respiratory tract and the upper digestive tract (ie upper aerodigestive tract), liver, colon, rectum and breast. Although the exact mechanism of ethanol-associated carcinogenesis still remains unknown, a number of factors may contribute to the development of alcohol-associated cancer, including ethanol metabolising enzymes. Ethanol is metabolised to acetaldehyde, the first and most toxic metabolite of alcohol, mainly by alcohol dehydrogenase (ADH) enzymes. Acetaldehyde is then metabolised to acetic acid by aldehyde dehydrogenases (ALDHs). A recent study in *Nature Genetics*[1] has indicated that genetic variants of ADH1B and ADH7 are protective against aerodigestive cancer. These protective effects were more evident with increasing alcohol consumption. In this issue of *Human Genomics*, Brooks *et al.*, in a guest editorial, describe how alcohol- and acetaldehyde-metabolising enzymes may modulate susceptibility to alcohol-induced oesophageal cancer. The ALDH2 gene product is a mitochondrial protein responsible for acetaldehyde clearance. There is a substantial body of evidence suggesting that the *ALDH2*2* allele protects against alcoholism and is a determinant of alcohol avoidance in some ethnic populations; however, a higher incidence of alcohol-induced cancers is associated with the *ALDH2*2* gene. Although the exact mechanism underlying these phenomena remains to be elucidated, it is currently believed that acetaldehyde accumulation may be responsible. Peng and Yin review how the different *ALDH2* genotypes affect venous blood acetaldehyde levels after various doses of ethanol intake.

Mutations in another aldehyde dehydrogenase gene (*ALDH5A1*) are the molecular basis for succinate semialdehyde dehydrogenase (SSADH) deficiency, which is a neurological disorder associated with developmental delay, prominent language deficits, hypotonia, ataxia, hyporeflexia and seizures. Malaspina and colleagues report on the comparative genomics of *ALDH5A1* and the accumulation of gamma-hydroxybutyrate associated with its deficiency. In another paper in this issue, Gherman *et al.* report on how the spatial configuration of neighbouring genes affects their regulation and function. Their systematic survey of the distribution and orientation of genes and the properties of intergenic intervals reveals previously unknown properties of the genome which will be the basis for further studies.

Shukla *et al.* have used the whole-genome approach with molecular experiments to identify factors involved in conferring cellular resistance to carboplatin, a chemotherapeutic agent used in the management of many cancers, but with treatment limited by resistance and toxicity. They have identified and validated the *CD44* gene as a major factor contributing to carboplatin resistance in tumour cell lines.

Garenc *et al.* report on the effects of the *LIPE* C-60G polymorphism on body fat, plasma lipid and lipoprotein concentrations, and its interaction with physical activity. Their results suggest that the associations between physical activity and body fat and plasma lipoprotein/lipid concentrations in men are dependent on the *LIPE* C-60G polymorphism. The study highlights the importance of taking into account the role of gene–physical activity interactions in candidate gene studies of obesity and obesity-related traits.

Matimba *et al.* describe novel SNPs of *CYP2C9, CYP2C19, CYP2D6* and *NAT2* genes in African populations. While confirming African-specific variants, they found only modest variation between different African ethnicities, indicating similar metabolic profiles for most drugs, yet stressing interindividual variability. Based on the generally high level of diversity in gene loci of African populations, the authors suggest that rare variants (incidence of less than 1 per cent) and interindividual variability might account for the phenotypic diversity in drug response occuring in the African population.

In the Software Review section, Plagnol reviews software available for copy number variation association testing for unrelated case control or family data.

Finally, in the Gene Annotation section, He *et al*. review the solute-carrier gene (*SLC*) superfamily that encodes membrane-bound transporters. This is a rather large superfamily, consisting of 55 gene families having at least 362 putatively functional genes coding for transporters, symporters and antiporters.

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Reference

1. Hashibe, M., McKay, J.D., Curado, M.P. *et al*. (2008), 'Multiple *ADH* genes are associated with upper aerodigestive cancers', *Nature Genetics* Vol. 40, pp. 707–709.