MEDICAL GENETICS: ADVANCES IN BRIEF

Mutations of the KIT (mast/stem cell growth factor receptor) proto-oncogene account for a continuous range of phenotypes in human piebaldism
Spritz RA, Holmes SA, Ramesar R, Greenberg J, Curtis D, Beighton P.
Am J Hum Genet 1992;51:1058–65.

In this paper Spritz *et al* report further mutations in the KIT proto-oncogene in families with autosomal dominant piebaldism. They also attempt to provide an explanation for the phenotypic variability in terms of the position of the mutations and their effect on the protein produced. The KIT proto-oncogene encodes the cellular receptor tyrosine kinase that functions as the transmembrane receptor for the mast/stem cell growth factor. It comprises an extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. The monomer dimerises in response to ligand binding and this step is thought to be crucial in signal transduction. Three previously described mutations in the tyrosine kinase binding domain have all led to a severe phenotype. Mutations in two families with variable phenotypes have been frameshifts that would stop translation near the beginning of the intracellular tyrosine kinase domain. In this paper two more mutations are reported. One proband has the mild phenotype and a frameshift that would lead to an extremely truncated protein with no transmembrane region and no tyrosine kinase domain. In the second family with a variable phenotype the mutation is at the 5′ splice site of IVS12. The authors' proposal is that mutations leading to simple loss of function result in a mild phenotype and mutations that interfere with formation of the heterodimer have a greater effect as the decrease in number of functional receptors will be more than 50%. Mutations that can cause a mixture of loss of function and interference with heterodimer formation may produce a variable phenotype within a family. It will be interesting to see if this hypothesis holds as further families are investigated.

JUDITH GOODSHIP

Continuum of overlapping clones spanning the entire human chromosome 21q
Chumakov I, Rigault P, Guillou S, *et al.*
Nature 1992;359:380–7.

A second-generation linkage map of the human genome
Weissenbach J, Gyapay G, Dib C, *et al.*
Nature 1992;359:794–801.

The era of Big Science has come to human genetics. That is the message from the first two major papers, published within four weeks of one another, to appear from Daniel Cohen's Généthon. Funded by public subscription through television advertisement, this 'gene factory' is organised as an assembly line of robots, operated by just five technicians (see *Nature* 1992;357:526–7). Fully operational for under a year, the robots have an astonishing capacity. They can sequence 500 cDNAs per week, or Southern blot 6000 DNA samples and prepare 300 000 yeast artificial chromosomes in a single day. The vast amount of data generated is automatically fed into powerful computers: by saturating the system with information, inevitable discrepancies (deleted YACs, mistyped polymorphisms) can largely be ironed out. The results speak for themselves. In Chumakov *et al*, sequence tagged sites (STSs) have been used to order physically 810 YAC clones in continuous array spanning the whole of chromosome 21q (40 to 50 megabases). Weissenbach *et al* describe a human genetic linkage map comprised entirely of $(CA)_n$ polymorphisms (814 of them), 74% having a heterozygosity >0.7. Both represent substantial advances for the Human Genome Project and have converted many scientists to the underlying factory philosophy. Plans for Généthon clones are advancing rapidly in the USA.

ANDREW WILKIE

Comparative genomic hybridization for molecular cytogenetic analysis of solid tumours
Kallioniemi A, Kallioniemi OP, Sudar D, *et al. Science* 1992;258:818–21.

A team from Dan Pinkel's laboratory here describe another advance in fluorescent in situ hybridisation. First, total tumour DNA and normal 'reference' DNA are isolated and labelled with different compounds (biotin and digoxigenin). Then the two are hybridised simultaneously to normal metaphase spreads from any source. Simultaneous detection (with FITC for biotin and rhodamine for digoxigenin) results in a green (FITC) to red (rhodamine) fluorescence ratio along the length of each chromosome; any increase in tumour copy number (duplication/trisomy) will increase the green component while any reduction (deletion/monosomy) will shift the ratio to the red. In cell lines, the method successfully detected whole chromosome aneuploidy, small interstitial cytogenetic deletions, and confirmed and corrected a complex breast cancer karyotype. Regions of known and previously unsuspected gene amplification were also shown in a variety of cancers. The new method provides a whole genome screen which is not limited by the technical difficulties of conventional solid tumour cytogenetics. In practice, however, the technique will critically depend on the heterogeneity of the target tumour tissue and the cost of the sophisticated image processing equipment required. Nevertheless the approach described opens up new possibilities within and beyond solid tumour genetics.

JOHN C K BARBER

Molecular basis of human hypertension: the role of angiotensinogen
Jeunemaitre X, Soubrier F, Kotelevtsev, *et al. Cell* 1992;71:169–80.

This paper reports on a genetic linkage between essential hypertension and the angiotensinogen (AGT) gene. Because hypertension is characterised by multifactorial determinants, the authors have tested for linkage in pairs of affected sibs. Statistically significant linkage was found in pooled hypertensive populations from two centres. A more significant linkage was shown in patients with severe hypertension. Linkage was only observed in male-male sib pairs. Molecular variants of AGT were characterised and two amino acid substitutions (both in exon 2 of the AGT gene) were shown to be significantly more frequent in hypertensive subjects than in controls. The two variants were also shown to be in linkage disequilibrium. Although linkage was not observed in female-female sib pairs, both the variants were significantly more frequent in hypertensive females than in controls. This suggests that AGT may contribute directly to hypertension risk in males but only indirectly in females. The latter could be because of effects of other oestrogen modulated factors on the renin-angiotensin system. Higher plasma concentrations of AGT were shown among the carriers of one of the variants. This together with the previous demonstration of positive correlation between plasma AGT levels and hypertension indicates a direct role for AGT and its variants in pathogenesis of essential hypertension.

N S THAKKER

Association between confined placental trisomy, fetal uniparental disomy and early intrauterine growth retardation
Bennett P, Vaughan J, Henderson D, Loughna S, Moore G. *Lancet* 1992;340:1284–5.

Uniparental disomy with normal phenotype
Dworniczak B, Koppers B, Kurlemann G, Holzgreve W, Horst J, Miny P. *Lancet* 1992;340:1285.

Dworniczak and colleagues observed placental trisomy 16 and maternal disomy 16 in a baby who had severe intrauterine growth retardation (IUGR). Subsequent development was normal at 3½ months, leading the authors to suggest that uniparental disomy may be compatible with normal development if "chromosomes not subject to imprinting are involved." Bennett *et al* report a pregnancy complicated by severe IUGR, from 23 weeks' gestation. Placental mosaic trisomy 16 was observed while fetal tissues were disomic for maternal 16. They contrast this case with another pregnancy in which growth retardation was a late (30 weeks +) feature. Inadequate umbilical perfusion consequent on placental haematoma is recorded as the likely cause of IUGR in this second case, in which placental trisomy 16 was recorded in all cells but without evidence of disomy in fetal tissues. The authors conclude that placental mosaicism may lead to growth disorders if associated with fetal disomy but may be compatible with normal growth if the fetus is normal. Uniparental disomy as a possible mechanism for unexplained IUGR is not a new idea, but whether resulting from fetal disomy per se or from placental mosaicism remains to be answered. Although both these letters to the Editor confirm that maternal disomy 16 is associated with unexplained IUGR, they do little to advance our knowledge and understanding as to why this might be. In particular, Bennett *et al* do not address the reasons why development and growth of the fetus they report was normal at 13 and 16 weeks with deterioration in growth only becoming apparent at 23 weeks. Is it reasonable to attribute this late phenomenon to an imprinting effect? Finally, the presentation of molecular data by Bennett *et al* is unusually poor and there is no accompanying explanation of dosage, upon which it clearly depends. Letters to the Editor may not be the ideal vehicle for exploring difficult concepts in genetics as they relate more broadly: they need not fall so wide of the mark.

W REARDON