nature genetics November

Receptor malfunction

The family of four fibroblast growth factor receptors is stimulating attention with the discovery of genetic defects tying three members to a variety of congenital bone malformations.

THE field of bone morphogenesis has undergone a revolution in the past few months with the discovery that no fewer than three members of the fibroblast growth factor receptor (FGFR) gene family are, when defective, involved in a variety of hereditary disorders of bone development, including achondroplasia, the most common form of human dwarfism. In each case, genetic mapping has rapidly led to the isolation of the genes responsible for achondroplasia[1, 2], Crouzon syndrome[3] and now, as described in this month's issue of *Nature Genetics*, Pfeiffer syndrome[4].

The first FGFR defect was found earlier this year, following the mapping by several groups of the locus for achondroplasia to the distal end of the short arm of chromosome 4. A candidate gene, *FGFR3*, lurking near the achondroplasia locus, had been examined but quickly discarded during the ten-year hunt for the Huntington's disease gene, but genetic analysis quickly showed that patients with achondroplasia harboured an identical missense mutation in the region of the gene encoding the transmembrane domain[1, 2]. This finding was all the more remarkable given the very high *de novo* rate of achondroplasia mutations.

At about the same time, Robin Winter and colleagues at the Institute of Child Health, London, discovered the gene for Crouzon syndrome[3], one of dozens of different malformations known as the craniosynostoses. These are disorders of variable severity in which the cranial sutures fail to fuse during development, leading to malformed skulls that often require major surgery; occasionally, there are also distal limb defects. Winter's group found that mutations in an alternatively spliced exon of *FGFR2* on chromosome 10, encoding an extracellular immunoglobulin-like domain, are responsible for many cases of Crouzon syndrome.

Sensing something of a trend, Maximilian Muenke (of the Children's Hospital, Philadelphia, and working in collaboration with Winter's group) realized when he mapped to chromosome 8 the locus for yet another related disorder, Pfeiffer syndrome, that the logical candidate in the area had to be the gene for a third FGFR molecule, *FGFR1*. In five apparently unrelated families with Pfeiffer syndrome, Muenke *et al.*[4] have discovered that the same mutation (a substitution of arginine for proline at residue 252), again in the extracellular portion of FGFR1, segregates with the disease.

Interestingly, Crouzon syndrome has just been shown to be allelic with Jackson–Weiss syndrome, which is characterized by hand and feet abnormalities as well as cranial disorders. Having studied the Amish kindred in which Jackson–Weiss syndrome was originally described, Jabs *et al.*[5] now report the finding of a mutation that lies just two residues away from one of the Crouzon syndrome substitutions.

These remarkable discoveries are certain to improve greatly our understanding of the developmental role of fibroblast growth factors and their receptors, studies of which until now have been largely confined to such lower organisms as *Drosophila* and *Xenopus*[6]. It is unlikely that progress will stop here: there are four known mammalian FGFRs and nine different fibroblast growth factors, suggesting that careful scrutiny of the loci for these factors and other dysmorphological syndromes will soon herald many fascinating discoveries.

A similar strategy to find candidate genes has also paid off handsomely in unravelling the molecular basis of a form of dystonia, as described elsewhere in this month's issue of *Nature Genetics*. Toshiharu Nagatsu and colleagues at Fujita Health University in Japan report the identification of four different mutations in the gene for GTP cyclohydrase I in patients with hereditary progressive dystonia[7]. This disorder, also known as DOPA-responsive dystonia, is characterized by a progressive movement disorder similar to Parkinson's disease, and was recently mapped to chromosome 14. The enzyme GTP cyclohydrase I catalyses a rate-limiting step in the biosynthesis of biopterin, a crucial cofactor for several different enzymes involved in the manufacture of dopamine. Ichinose *et al.*[7] have mapped the GTP cyclohydrase I gene to chromosome 14, and show that four patients with DOPA-responsive dystonia carry mutations in this gene; in at least two cases these mutations completely destroy the activity of the enzyme.

Elsewhere in Japan, researchers at Kyoto University led by Akira Kakizuka have uncovered another example of an expansion of a CAG trinucleotide repeat, in this instance one responsible for the neurodegenerative condition Machado–Joseph disease[8]. The gene encodes a protein of 359 amino acids that has no familiar features other than the putative polyglutamine stretch of 13 to 36 residues towards the carboxy-terminal end. But in individuals affected with this dominant progressive disorder, which bears many similarities to Huntington's disease and spinocerebellar ataxia (SCA), this segment has as many as 79 repeats.

Five loci for spinocerebellar ataxia have now been genetically mapped in humans, thanks to the discovery by Ranum *et al.*[9], reported in this issue, of the chromosomal assignment of *SCA5*. This may seem fairly unremarkable in itself, but the same cannot be said for the pedigree that enabled the gene to be mapped: the trait was evidently passed down by the paternal grandparents of President Abraham Lincoln. Two of the president's father's siblings inherited the errant gene for SCA5, and study of their extended families has allowed Ranum *et al.* to localize the gene to chromosome 11.

President Lincoln was the subject of genetical speculation a few years ago: when the gene for Marfan syndrome was isolated, it was suggested that he might have suffered from this condition. He was assassinated at the age of 56 and has no living direct descendents. But noting that SCA5 is a fairly mild, late-onset form of ataxia, Ranum and colleagues cannot resist asking whether the president might perhaps have inherited the faulty version of this gene too.

Kevin Davies

Kevin Davies is *Editor of* Nature Genetics.

Also in this month's *Nature Genetics*: a new syndrome involving interchange of the long arms of the X and Y chromosomes; mutations in the human homologue of microphthalmia cause Waardenburg syndrome type 2; CGG triplet repeat expansion in FRAXF; a possible locus for bipolar affective disorder; and identification of the Xg blood group.

1. Shiang, R. *et al. Cell* **78**, 335–342 (1994).
2. Rousseau, F. *et al. Nature* **371**, 252–254 (1994).
3. Reardon, W. *et al. Nature Genet.* **8**, 98–103 (1994).
4. Muenke, M. *et al. Nature Genet.* **8**, 269–274 (1994).
5. Jabs, E.W. *et al. Nature Genet.* **8**, 275–279 (1994).
6. Mason, I. J. *Cell* **78**, 547–552 (1994).
7. Ichinose, H. *et al. Nature Genet.* **8**, 236–242 (1994).
8. Kawaguchi, Y. *et al. Nature Genet.* **8**, 221–228 (1994).
9. Ranum, L. P. W., Schut, L. J., Lundgren, J. K., Orr, H. T. & Livingston, D. M. *Nature Genet.* **8**, 280–284 (1994).