embryo, such as *Hoxa13* and *Hoxd13*, are recoverable because the anterior equivalents are likely to be embryonic lethal.

Recent years have seen an explosion in our understanding of the genetic basis for developmental processes. As developmental genes are uncovered and their positions mapped in the genome, they quickly become candidates for disease genes[9]. This has led, for example, to the identification of a mutation in the *MSX1* gene, which is related to the *HOX* genes, as the cause of tooth agenesis[10]. Likewise, *Patched*, a gene involved in the Hedgehog signaling pathway, has recently been found to be mutated in Gorlin syndrome[11] (see Box). As more is learned about embryogenesis and the genes involved in development, further insights into medical genetics are bound to follow.

1. Mortlock, D.P. *et al. Nature Genet.* **13**, 284–289 (1996).
2. Muragaki, Y. *et al. Science* **272**, 548–551 (1996).
3. Han, K. & Manley J.L. *Genes Dev.* **7**, 491–503 (1993).
4. Han, K. & Manley, J.L. *EMBO J.* **12**, 2723–2733 (1993).
5. Bates, G. & Lehrach, H. *BioEssays* **16**, 277–284 (1994).
6. Dolle, P. *et al. Cell* **75**, 431–441 (1993).
7. Davis, A.P. & Capecchi, M.R. *Development* **122**, 1175–1185 (1996).
8. Hyduk, D. & Percival-Smith, A. *Genetics* **142**, 481–492 (1996).
9. Banfi, S. *et al. Nature Genet.* **13**, 167–174 (1996).
10. Vastardis, H. *et al Nature Genet.* (in the press).
11. Wicking, C. *et al. Cell* (in the press).

Box Cancer and development patched together

In another example of the emerging parallels between developmental genetics and human genetic disorders, two teams report in *Cell*[1] and *Science*[2] that they have identified the gene for Gorlin syndrome (or nevoid basal cell carcinoma syndrome) as the human homologue of the *Patched* gene in *Drosophila*, and may tie in with recent discoveries linking other *Drosophila* developmental genes in carcinogenesis. Patients with Gorlin syndrome have increased risk for a variety of basal cell and other cancers, but in addition exhibit a variety of developmental and skeletal defects including spina bifida and jaw cysts (see Fig. 1).

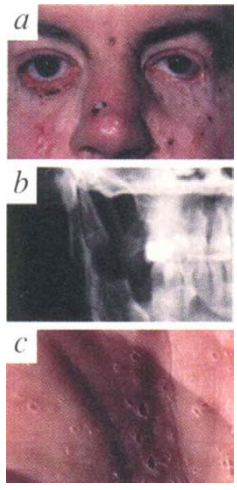

Fig. 1 Key features of the nevoid basal cell carcinoma syndrome include multiple basal cell carcinomas, which appear as pearly or crusted lesions (top), keratocysts of the jaw (middle), and palmar pits (bottom). In addition, affected individuals have bifid ribs, spine anomalies and malformations of midline stuctures of the brain.

Hahn *et al.* conducted a gruelling search of a 2-megabase region of chromosome 9q22 for the Gorlin gene before eventually settling on *PTC*, a 22-exon gene showing 67% similarity to *Patched* at the DNA level[3]. The authors describe six frameshift and nonsense mutations in affected patients (including a *de novo* mutation not observed in the patient's parents), and an additional pair of mutations in the remaining allele in two patients with sporadic basal cell carcinomas (BCC) and allelic loss of the critical region[1].

In a separate study (submitted while Hahn *et al.* was 'in press'), Johnson *et al.* undertook a 'positional candidate' approach, isolating the human *Patched* gene and localizing it to the NBCC region. They identified a 9-bp insertion and an 11-bp deletion in two families with NBCC, and a missense mutation in one out of 12 BCC patients[2].

PTC is a transmembrane glycoprotein which, in *Drosophila*, antagonizes the *hedgehog*-mediated induction of several genes involved in cell–cell communication and signalling, including *decapentaplegic* (*dpp*) and curiously *ptc* itself. Matthew Scott and colleagues at Stanford, co-authors of the *Science* paper, recently demonstrated that this pathway is conserved in mice, and speculated that "lost *ptc* function in vertebrates will lead to ectopic expression of many [*hedgehog*] targets"[4]. This could have important ramifications for the TGF-β signalling pathway[5] in the skin, for example. That is because Dpp is a member of the TGF-β/bone morphogenesis protein family which, after induction, signals other cells through a pathway[5] that is still being worked out but which includes the *mad* (mothers against *dpp*) gene product[6]. A human homologue of *mad*, *DPC4*, was recently identified as a putative tumour suppressor gene on chromosome 18q in pancreatic cancer[7].

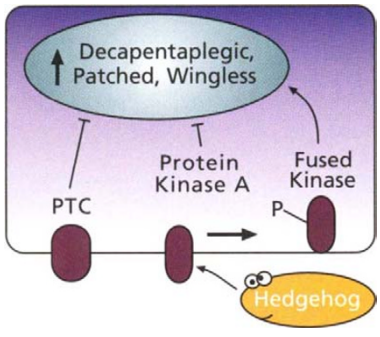

Fig. 2 Simplified diagram of hedgehog/patched signalling pathway. Patched represses the induction of gene expression controlled by hedgehog. Patched inhibition involves protein kinase A among other proteins.

These findings are complemented by two papers from Bert Vogelstein and colleagues at Johns Hopkins University in this issue[8,9]. On page 347, they describe the cloning and localization of five new human homologues of the *mad* gene (in addition to *DPC4*). One of them, *JV18-1*, maps to the region of chromosome 18q that is commonly lost in colorectal cancer, about 3 Mb proximal to *DPC4*, and is shown to be somatically mutated in two out of 18 colorectal cancers examined. In an accompanying paper (page 343)[9], the Vogelstein group shows that *DPC4* itself is mutated in about one third of colon cancers that have lost the long arm of chromosome 18, expanding the role of this *mad* homologue in carcinogenesis. Further advances will not be far away as the links between Patched and its developmental partners and their roles in growth control and carcinogenesis are defined.

— Kevin Davies

1. Hahn, H. *et al. Cell*, 14 June (1996).
2. Johnson, R.L. *et al. Science* **272**, 1668-1671 (1996).
3. Hahn, H. *et al. J. Biol. Chem.* (in the press).
4. Goodrich, L.V. *et al. Genes Dev.* **10**, 301-312 (1996).
5. Serra, R. & Moses, H.L. *Nature Med.* **2**, 390-391 (1996).
6. Sekelsky, J.J. *et al. Genetics* **139**, 1347-1358 (1995).
7. Hahn, S.A. *et al. Science* **271**, 350-353 (1996).
8. Riggins, G.J. *et al. Nature Genet.* **13**, 347–349.(1996).
9. Thiagalingam, S. *et al. Nature Genet.* **13**, 343–346.(1996).