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Fingering fibroblast growth factor receptors

When the sites of the genes for achondroplasia (ACH)[1,2] and Crouzon craniofacial dysostosis (CFD)[3] were revealed in *Nature Genetics* just a few months ago, it was only natural to believe that it would take years to identify the genes themselves. After all, the *ACH* gene was believed to map within a critical region of about 2.5 megabases at the tip of chromosome 4p (ref. 4), and *CFD* had only been assigned to chromosome 10q25–26. But in two remarkable publications that are related by more than the speed with which they were completed, the surprising culprits have been found. Writing in *Cell*[5], John Wasmuth's group at the University of California, Irvine, show that mutations at a single residue in the fibroblast growth factor receptor 3 (FGFR3) give rise to ACH. And now, on page 98 of this issue of *Nature Genetics*, William Reardon, Robin Winter and colleagues at the Institute of Child Health in London implicate a closely related member of the same family, fibro-blast growth factor receptor 2 (*FGFR2*), in Crouzon syndrome[6].

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Fig. 1 Alexandre Schafnitz, 4, at the press conference announcing the discovery of the achondroplasia gene.

Achondroplasia, the most common genetic form of dwarfism, is a notable disorder for several reasons. It has one of the highest known rates of sporadic mutation known — about four out of five cases are thought to arise *de novo*. The ACH mutation does not act as a 'true' dominant: heterozygotes exhibit a characteristic phenotype of rhizomelic dwarfism, most pronounced in the proximal limbs. By contrast, the homozygous form frequently results in death at or shortly after birth. Crouzon syndrome, characterized by the premature fusion of the facial bone sutures, is probably the best known of dozens of different craniosynostoses, although the molecular defects in two similar disorders — Grieg cephalopoly-syndactily and craniosynostosis (Boston type) — have been identified[7,8].

A few months ago, the *ACH* locus was assigned to the terminal portion of chromosome 4p, somewhere between the gene for Huntington's disease and the telomere. Wasmuth's group had been a part of the consortium that successfully cloned the Huntington's gene last year, and followed that by defining the molecular basis for hyperekplexia — familial startle syndrome — last December[9]. But although the Huntington's work had been backbreaking, requiring the construction of extensive physical maps and the study of many candidate genes, that monumental effort has paid off again in an unexpected fashion.

Among the genes which Wasmuth's team had mapped (and excluded from *HD*) was *FGFR3*, which codes for one of four closely related fibroblast growth factor receptors with a diverse pattern of tissue-specific expression. *FGFR3* is expressed in the prebone cartilage rudiments, but it is also expressed widely in the central nervous system, which detracted somewhat from its candidacy in ACH. Nevertheless, Wasmuth's intuition that *FGFR3* might be responsible for ACH paid off, just weeks into his group's search. Not only did they detect a point mutation in each of 16 ACH chromosomes examined, but in every case, the mutation occurred at the same nucleotide (1138) of *FGFR3*. In 15/16 chromosomes, the mutation was a G to A transition; in every case, the result was a Gly380Arg substitution in the solitary transmembrane domain of the receptor. Wasmuth's group also noted the same mutation in three sporadic ACH patients, whose parents were all homozygous for the wild-type allele.

Crouzon's connection. Whereas *FGFR3* had been suggested early on as a possible candidate for ACH, little attention was focused on its homologue, *FGFR2*, when CFD was linked to distal chromosome 10q. This was largely because a number of more enticing transcription factor genes, such as *PAX2*, mapped to the same region. But Reardon *et al.*[6], noting that an alternatively spliced product of the mouse *Fgfr2* gene is prominently expressed in osteogenesis, chose to focus on its human counterpart. Concentrating on just the 49-amino-acid, alternatively spliced B exon of *FGFR2*, which encodes part of the third extracellular immunoglobulin-like (Ig) domain, Reardon *et al.* detected a striking pattern of sequence alterations using single-strand conformational polymorphism analysis (SSCP). Nine out of twenty familial and sporadic cases of CFD exhibited SSCP changes, whereas none out of 178 controls did so. It turns out that seven of these mutations alter amino acids (usually a cysteine) in the third Ig domain of FGFR2. The other two nucleotide changes are silent, but, as they are not found in normal controls, may affect splicing of the gene. A more extensive screening of *FGFR2* should uncover additional CFD mutations.

These exciting findings raise many interesting questions, such as why a simple missense mutation in fibroblast growth factor receptors should give rise to two dominant phenotypes? One possibility is that the mutation interferes with the process of dimerization, which occurs on activation, or somehow constitutively activates the ensuing signal transduction cascade. Also unresolved for the moment is the possibility that other lesions in the two receptors explain other genetic disorders. *FGFR3* will be examined for mutations in hypochondroplasia, a milder form of dwarfism that may well be allelic to ACH[2]. It will also be interesting to see if *FGFR2* is mutated in Jackson-Weiss syndrome, which (in at least one form) also maps to chromosome 10q (ref. 10). Finally, a longer-term issue is why the phenotypes of ACH and CFD should be confined to bone abnormalities, even though the defective genes are expressed in a broad range of cell types.

The intriguing clustering of both sets of mutations in the transmembrane and extracellular coding portions of *FGFR3* and *FGFR2* respectively, and the availability of simple restriction enzyme assays to detect them, will undoubtedly facilitate genetic screening tests. But the ethical dilemmas associated with ACH in particular are considerable. While Wasmuth's team believes, as do many, that prenatal diagnosis for the homozygous form of ACH is thoroughly justified (owing to the severity of the condition and risks of pregnancy for the mother[4,5]), they abhor any other possible uses of prenatal screening for ACH, which after all affects only a person's physical stature. Says David Brookfield, of the Little People of America: "I don't want to be alive when the last dwarf is born". But the desire of some ACH parents to have similarly affected children may also lead to a potentially dangerous situation. Two ACH parents have a 50% chance of having an ACH (heterozygous) child, and in some cases ACH parents might prefer to raise a dwarf child with ACH rather than a 'normal' child of average height. It is yet another counselling conundrum fueled by the rapid pace of genetic discovery.

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