IN BRIEF

ANIMAL MODELS

Identification and functional analysis of mutation in the hypocretin (orexin) genes of narcoleptic canines.

Hungs, M. *et al. Genome Res.* **11**, 531–539 (2001)

In dobermans and labradors, familial narcolepsy is caused by mutations in hypocretin receptor 2 (*Hcrtr2*), but most familial and sporadic cases of human narcolepsy lack mutations in hypocretin (*Hcrt*) and its receptors. In this study of the dog *Hcrtr2* and *Hcrt* loci in familial and sporadic cases of canine narcolepsy, only one further mutation was identified. The lack of mutations at these genes in sporadic cases indicates that this form of narcolepsy is genetically heterogeneous in dogs, as it is in humans.

HUMAN GENETICS

Neuronal sodium-channel α1 subunit mutations in generalized epilepsy with febrile seizures plus.

Wallace, R. H. *et al. Am. J. Hum. Genet.* **68**, 859–865 (2001)

A novel *SCN1A* mutation associated with generalized epilepsy with febrile seizures plus — and prevalence of variants in patients with epilepsy.

Escayg, A. *et al. Am. J. Hum. Genet.* **68**, 866–873 (2001)

Generalized epilepsy with febrile seizures plus (GEFS+) is a syndrome that shows genetic heterogeneity and a highly variable phenotype. Some cases of GEFS+ are caused by mutations that affect subunits of a sodium channel (SCN1A and SCN1B), and lead to reduced channel inactivation and increased neuronal excitability. To test whether *SCN1A* mutations could cause more common forms of epilepsy, Escayg *et al.* screened 226 patients with a range of phenotypes. Several variants of the *SCN1A* gene were identified, but functional studies will be needed to test their relevance. Meanwhile, by screening a further 36 GEFS+ families, Wallace *et al.* show that the sodium-channel defects could account for ~17% of familial cases. Overall, sodium-channel defects are an important cause of some forms of epilepsy, and these studies will encourage the analysis of genes that encode other sodium-channel subunits or interacting proteins.

HUMAN DISEASE

A major susceptibility locus for leprosy in India maps to chromosome 10p13.

Siddiqui, M. R. *et al. Nature Genet.* **27**, 439–441 (2001)

Half of the world's 800,000 cases of leprosy — a chronic infectious disease that is caused by the pathogenic bacterium *Mycobacterium leprae* — occur in India. A genetic linkage scan of affected sib-pairs, from 224 families in South India with 396 microsatellite markers, revealed a significant linkage of a major susceptibilty locus to markers on chromosome 10p13. This study proves that genome-wide linkage analysis can be used to identify major loci even in cases, such as this, in which the genetic component to susceptibility would be expected to be highly polygenic.

MOUSE MODELS

Discriminating cuts

Normal development depends crucially on precise communication between embryonic tissues, which in turn depends on finely tuned gene expression. But how do cells discriminate between the signals of a large family of ligands that are often co-expressed? In such cases, signalling specificity can be imposed by tightly regulating the expression of receptors with different affinities. Tissue-specific alternative splicing can achieve this — and is the focus of a recent paper in which the inactivation of one isoform of mouse Fgfr2 (fibroblast growth factor receptor 2) had disastrous developmental consequences, producing defects similar to the human Apert and Pfeiffer syndromes. These disorders are characterized by craniosynostosis (the premature closure of cranial sutures) and short stature.

Four Fgf receptors transduce signals from ~22 Fgf ligands during mammalian development, requiring that receptor affinity and specificity be tightly regulated. This is brought about by the alternative splicing of exons that encode the extracellular domains (loops I–III) of each Fgfr. This splicing generates different receptor isoforms (called a, b or c), each with distinct ligand-binding affinities. For *Fgfr2*, this splicing is highly tissue specific — in epithelial tissue, exons 7, 8 and 10 are used to generate the Fgfr2IIIb isoform, and in mesenchymal tissue, exons 7, 9 and 10 create the Fgfr2IIIc isoform. Reciprocal signalling occurs because epithelially expressed Fgfs activate only the mesenchymally spliced Fgfr2IIIc, and mesenchymally expressed Fgfs activate only epithelial Fgfr2IIIb.

Patients with Apert syndrome commonly have *FGFR2* mutations in these extracellular regions generated by alternative splicing — mutations that might, according to previous work, create a mutant form of *FGFR2IIIc* that aberrantly responds to mesenchymally expressed FGFs. However, Hajihosseini *et al.* have now found that abrogating the expression of the *Fgfr2IIIc* isoform in mice, by deleting exon 9 from mouse *Fgfr2*, results in a dominant gain of function that causes premature ossification of the cranial sutures and intersternebral cartilage, and defects in organs that undergo branching morphogenesis. This mutant phenotype recapitulates many features of the Apert and Pfeiffer syndromes.

How can loss of *Fgfr2IIIc* result in the same defects that are caused by mutations that alter the activity of *FGFR2IIIc*? Hajihosseini *et al.* found that deletion of exon 9 leads to the upregulated expression of the *Fgfr2IIIb* isoform in cells that normally express *Fgfr2IIIc*, which causes those cells to respond to the wrong Fgfs. The mesenchymal expression of *Fgfr2IIIb* disrupts the epithelial–mesenchymal reciprocal signalling required for branching morphogenesis. And because *Fgfr2IIIb* signalling probably also mediates normal endochondrial bone formation, its ectopic activation might underlie the abnormal and excessive bone ossification in these mutant mice. Future work should pinpoint whether other Fgf-related developmental disorders are caused by similar ligand-independent, receptor-activation mechanisms.

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References and links

ORIGINAL RESEARCH PAPER Hajihosseini, M. K. *et al.* A splicing switch and gain-of-function mutation in *FgfR2-IIIc* hemizgotes causes Apert/Pfeiffer-syndrome-like phenotypes. *Proc. Natl Acad. Sci. USA* **98**, 3855–3860 (2001)
FURTHER READING Yu, K. & Ornitz, D. M. Uncoupling fibroblast growth factor receptor 2 ligand binding specificty leads to Apert syndrome-like phenotypes. *Proc. Natl Acad. Sci. USA* **98**, 3641–3643 (2001)
WEB SITE Craniosynostosis syndromes