IN THE NEWS

Moral low ground

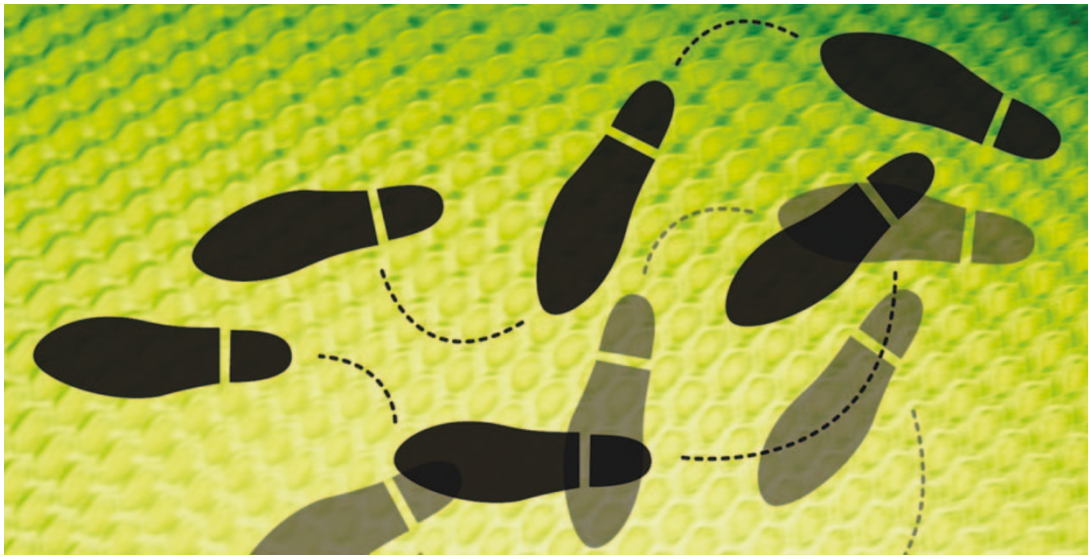
The European Patent Office (EPO) has upheld a patent relating to the testing of Ashkenazi-Jewish women for a particular mutation in *BRCA2*.

The mutation — 6974delT, the focus of the patent originally filed by the Utah based biotech firm Myriad Genetics — occurs frequently in the Ashkenazi-Jewish population, making the claim in terms of patent law an inventive, novel and industrially applicable one. Gert Matthijs, Chair of the European Society for Human Genetics (ESHG) Patenting and Licensing committee said, "We understand the EPO had to decide about this case within the constraints of the patent law … nevertheless we still believe that there is something fundamentally wrong if one ethnic group can be singled out by patenting" (http://www.mydna.com, 5 July 2005).

One in 100 Ashkenazi-Jewish women has this mutation, which gives a 65–70% chance of developing breast cancer. Essentially, when a woman needs to be tested for the 6974delT mutation, this will be free unless she is known to be Ashkenazi-Jewish. "What it means in practice is that genetic centres that do not have licences for this test — or where the healthcare systems cannot afford to pay for it — may be forced to deny it to Ashkenazi-Jewish women" said Gert-Jan van Ommen, from Leiden University Medical Centre (http://www.the-scientist.com, 1 July 2005).

The EPO has granted patents on hundreds of genes, but few patent holders, unlike the holders of this *BRCA2* patent, have requested licence fees from public health centres in Europe. As Mary Rice from the ESHG concludes, this is now "...a moral not a legal issue" and opponents will have to mount further challenges based on this fact (http://www.nature.com, 7 July 2005).

Nicola McCarthy



TUMORIGENESIS

JUN steps in

The activity of the transcription factor c-JUN is increased in several human cancers. In their *Nature* paper, Axel Behrens and colleagues now show that c-JUN is part of a transcriptional complex that is central to the development of colorectal cancer.

Loss of the adenomatous polyposis coli gene (*APC*) predisposes individuals to an increased risk of developing colorectal cancer. APC binds to axin and the glycogen synthase kinase GSK3β, and this complex phosphorylates the transcription regulator β-catenin, marking it for ubiquitylation and degradation. Only when WNT binds to its receptor Frizzled is this complex disrupted, allowing β-catenin to accumulate in the nucleus. Here it interacts with members of the transcription-factor family T-cell factor/lymphoid enhancing factor (TCF/LEF). WNT signalling can also affect other pathways including activation of the c-JUN N-terminal kinases (JNKs) that activate c-JUN by phosphorylating its N-terminus. The authors had previously identified factors that bind specifically to phosphorylated c-JUN and one of these was TCF4. As TCF4 can also interact with β-catenin, the authors investigated the interaction of TCF4 with both β-catenin and c-JUN. They found that the interaction of TCF4 with c-JUN is dependent on the phosphorylation of two N-terminal serines (Ser63 and Ser73) in c-JUN, and that TCF4 can bind both β-catenin and c-JUN simultaneously.

c-JUN autoregulates its own transcription by binding to two proximal sites in its own promoter. Interestingly, c-*JUN* also has a TCF consensus binding sequence upstream of these sites. The authors therefore investigated the regulation of c-*JUN* transcription, the efficiency of which, they found, was dependent on JNK and required an intact c-JUN–TCF4–β-catenin complex.

To study the biological consequences of the c-JUN–TCF4–β-catenin complex, the authors used the $Apc^{Min/+}$ mouse, which lacks one functional *Apc* allele and develops multiple intestinal neoplasias because of the subsequent loss of the wild-type allele. They bred these mice with Jun^{AA} mice, in which Ser63 and Ser73 of c-JUN are changed to alanines and so cannot bind TCF4. $Apc^{Min/+}Jun^{+/+}$ and $Apc^{Min/+}Jun^{AA/+}$ mice all developed intestinal neoplasia, but $Apc^{Min/+}Jun^{AA/AA}$ homozygotes developed intestinal cancer at a significantly slower rate. The tumours in these animals were also smaller and less frequent. This was caused by the significantly decreased proliferative index of the $Apc^{Min/+}Jun^{AA/AA}$ homozygote tumour cells.

What happens if c-*Jun* is deleted from the intestinal cells in $Apc^{Min/+}$ mice? These animals did not develop intestinal neoplasia, but instead had multiple cystic structures throughout the gut. The cysts showed accumulation of β-catenin, due to APC loss, as did the tumours in c-*Jun* wild-type $Apc^{Min/+}$ mice. The authors concluded that in the absence of c-*Jun*, activation of the β-catenin pathway is incapable of triggering tumour development, but instead causes formation of benign cysts.

As Jun^{AA} homozygous mice have normal development and lifespan, inhibition of the phospho-c-JUN–TCF4 interaction could be a possible target for the treatment of intestinal cancer.

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References and links

ORIGINAL RESEARCH PAPER Nateri, A. S., Spencer-Dene, B. & Behrens, A. Interaction of phosphorylated c-Jun with TCF4 regulates intestinal cancer development. *Nature* 10 July 2005 (doi:10.1038/nature03914)