allele that also carried the Leu217/Thr541 variants, and the authors hypothesized that the combined effect of three missense alterations would give rise to a highly penetrant *ELAC2* mutant. Notably, the triple-change was also present in an ovarian cancer patient of this family, which also included an ovarian cancer patient with the Leu217/Thr541 allele.

Identification of the *ELAC2* gene has left us with more questions than answers, and confirmatory studies need to be performed before it can be called a major prostate cancer susceptibility gene. However, the sequence similarity between *ELAC2* and DNA interstrand crosslink repair proteins PSO2 (SMN1) is intriguing in light of the established connection between DNA repair deficiency and cancer susceptibility. Interestingly, from a clinical point of view, alkylating drugs such as mitomycin C—at times used in treatment of advanced prostate cancer—are known to exert their cytotoxic effect by inducing DNA crosslink formation. It would be useful to further investigate whether the *ELAC2* product and its allelic variants have a role in repair of interstrand crosslinks or DNA damage caused by other carcinogens.

1. Carter, B.S., Beaty, T.H., Steinberg, G.D., Childs, B. & Walsh, P.C. Mendelian inheritance of familial prostate cancer. *Proc. Natl. Acad. Sci. USA* **89**, 3367–3371 (1992).
2. Tavtigian, S.V. *et al.* A strong candidate prostate cancer susceptibility gene at chromosome 17p. *Nature Genet.* **27**, 172-180 (2001).
3. Ross, R.K. *et al.* Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. *Cancer Res.* **58**, 4497–4504 (1998).
4. Wadelius, M., Andersson, A.O., Johansson, J.E., Wadelius C. & Rane, E. Prostate cancer associated with CYP17 genotype. *Pharmacogenet.* **9**, 635–639 (1999).
5. Irvine, R.A., Yu, M.C., Ross, R.K. & Coetzee, G.A. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res.* **55**, 1937–1940 (1995).
6. Mononen, N. *et al.* Two percent of Finnish prostate cancer patients have a germ-line mutation in the hormone-binding domain of the androgen receptor gene. *Cancer Res.* **60**, 6479–6481 (2000).
7. Xue, W. *et al.* Susceptibility to prostate cancer: interaction between genotypes at the androgen receptor and prostate-specific antigen loci. *Cancer Res.* **60**, 839–841 (2000).
8. Rebbeck, T.R. *et al.* Association of HPC2/ELAC2 genotypes and prostate cancer. *Am. J. Hum. Genet.* **67**, 1014–1019 (2000).
9. Smith, J.R. *et al.* Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* **274**, 1371–1374 (1996).
10. Berthon, P. *et al.* Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. *Am. J. Hum. Genet.* **62**, 1416–1424 (1998).
11. Gibbs, M. *et al.* Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. *Am. J. Hum. Genet.* **64**, 776–787 (1999).
12. Xu, J. *et al.* Evidence for a prostate cancer susceptibility locus on the X chromosome. *Nature Genet.* **20**, 175–179 (1998).
13. Gayther, S.A. *et al.* The frequency of germ-line mutations in the breast cancer predisposition genes BRCA1 and BRCA2 in familial prostate cancer. *Cancer Res.* **60**, 4513–4518 (2000).
14. Berry, R. *et al.* Evidence for a prostate cancer-susceptibility locus on chromosome 20. *Am. J. Hum. Genet.* **67**, 82–91 (2000).
15. Xu, L.L. *et al.* A novel androgen-regulated gene, PMEPA1, located on chromosome 20q13 exhibits high level expression in prostate. *Genomics* **66**, 257–263 (2000).
16. Gibbs, M. *et al.* A genomic scan of families with prostate cancer identifies multiple regions of interest. *Am. J. Hum. Genet.* **67**, 100–109 (2000).
17. Suarez, B.K. *et al.* A genome screen of multiplex sibships with prostate cancer. *Am. J. Hum. Genet.* **66**, 933–944 (2000).

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Spider venom helps hearts keep their rhythm

Although the sight of a large hairy spider is enough to give some people a heart attack, spider venom may eventually be used to treat some heart conditions. In the 4 January issue of *Nature*, Bode *et al.* (*Nature*, **409**, 35–36) report that a peptide isolated from the venom of the spider *Grammostola spatulata* (picture) inhibits atrial fibrillation. Atrial fibrillation, characterized by disorganized atrial activity, occurs in patients suffering from valve disease, hypertension, and chronic lung disease. It is the most common form of cardiac arrhythmia, and can lead to further complications such as hypotension, pulmonary congestion, strokes and angina pectoris.

The anti-arrhythmic effects of this peptide were discovered serendipitously in a research project that initially had nothing to do with hearts or spiders. Frederick Sachs, senior author on the study, began investigating mechanosensitive ion channels over 15 years ago. In a search for agents that block or activate mechanical sensitivity, his group began screening insect venoms, which are known to contain a variety of neuroactive compounds. "We tried a variety of spider and scorpion venoms in patch clamp experiments, and finally found two that inhibited mechanosensitive ion channel activity," said Sachs. Fractionation of the venom led to the isolation of a peptide from tarantula venom, GxMtx-4, that the authors observed to block the activity of cationic stretch-activated ion channels (SACs) in adult astrocytes and cardiocytes.

SACs convert gradients of stress into gradients of electrical activity, and sustained mechanical gradients can develop when systolic pressure and wall tension are high, conditions that are present in the diseased heart. "It was well-known that cardiac wall stretch increases heart rate, and we knew that these receptors were expressed in heart cells," said Sachs. He teamed up with Frank Bode and Mike Franz at Georgetown University to show that the peptide suppressed both the incidence and duration of atrial fibrillation in rabbit hearts. They also showed that GxMtx-4 acts only during stretch activation, as it has no effect on the action potential of resting atrial cells. "It also seems to have no acute effects on normal hearts in the absence of distension," added Sachs, although further toxicity analysis is required.

This finding of Bode *et al.* constitutes the first demonstration that SAC activation can generate atrial fibrillation. The authors therefore suggest that GsMtx-4 initiates a new class of anti-arrhythmic agents that could act on the cause, rather than the effects of cardiac arrhythmias.

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