BREAST CANCER

Checkmate

If breast cancer genetics were a game of chess, we wouldn't be close to winning it yet. We've taken two pieces off the board — *BRCA1* and *BRCA2* — but mutations in these genes account for only a small fraction of breast cancers. Hanne Meijers-Heijboers *et al.* have now claimed another pawn: they report in *Nature Genetics* that a truncating mutation in a cell-cycle checkpoint kinase, called CHEK2, might be responsible for 1% of all female breast cancer cases and 9% of all male breast cancer cases.

The authors screened families that did not have mutations in either *BRCA1* or *BRCA2*, but did have a history of breast cancer, for the *CHEK2**1100delC mutation. This mutant gene yields a protein that is devoid of kinase activity *in vitro*. Of the 1,071 individuals screened, 55 (5.1%) carried the *CHEK2**1100delC mutation, compared with only 18 of 1,620 (1.1%) control individuals. When these numbers were broken down further, a striking 13.5% of individuals from families that included cases of male breast cancer carried the variant. The authors conclude that in breast cancer families without *BRCA1* or *BRCA2* mutations, *CHEK2**1100delC confers a twofold increased risk of breast cancer in women and a tenfold increased risk in men.

The mutation does not increase the risk of breast cancer in people carrying mutations in *BRCA1* or *BRCA2*. This is consistent with previous studies showing that BRCA1 and CHEK2 participate in the same biochemical pathway, and also indicates that CHEK2 might share a common biochemical pathway with BRCA2.

The CHEK2 protein is activated by the DNA-damage-activated kinase ATM. CHEK2 blocks entry into mitosis at the G2 phase by activating p53 and inhibiting the pro-mitotic tyrosine phosphatase CDC25C. Consequently, cells with null mutations in *CHEK2* cannot stop and repair damaged DNA; this leads to genomic instability and, potentially, cancer.

So far, the authors have screened only for the *CHEK2**1100delC mutation; other mutations in the same gene might also be expected to contribute to breast cancer risk, with varying penetrance depending on the severity of the mutation. So, the finding of this low-penetrance susceptibility gene for breast cancer might allow us to remove several pieces from the chess board.

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References and links

ORIGINAL RESEARCH PAPER Meijers-Heijboer, H. *et al.* Low-penetrance susceptibility to breast cancer due to *CHEK2**1100delC in noncarriers of *BRCA1* and *BRCA2* mutations. *Nature Genet.* **31**, 55–59 (2002)

DIAGNOSTICS

Don't take the p…

A simple urine test to detect cancer at an early stage is every oncologist's dream, but for childhood neuroblastoma, for which just such a test is available, two groups report that it doesn't save lives.

These common childhood tumours produce catecholamines, the metabolites of which can be measured in urine. This forms the basis of a diagnostic test that is mandatory in Japan. But the validity of the study that first showed the test to improve survival has been questioned because data from the control group were collected before data from the screened group. Furthermore, childhood neuroblastoma can regress spontaneously, so detecting these tumours might actually increase mortality from unnecessary surgery.

Two groups have now compared large populations of screened and unscreened babies contemporaneously. William G. Woods and colleagues screened over 425,000 babies in the Quebec province, Canada, at three weeks and six months of age and followed them until the age of 8. Compared with four different populations of unscreened children, the cumulative mortality rate from neuroblastoma was no lower in the screened group. Moreover, the test failed to detect almost all the tumours with poor prognostic indicators, such as *MYCN* amplifications.

Freimut Schilling and colleagues screened nearly 1.5 million babies at one year of age in six states in Germany, and compared the incidence of late-stage neuroblastoma (stage 4) and mortality with that in babies born at the same time in the other ten states. The incidence of stage-4 neuroblastoma and mortality were the same in the screened and unscreened groups, despite the fact that more neuroblastomas were detected in the screened population.

Both studies therefore argue against population screening for neuroblastoma in infancy. They also highlight the need for more research into the two forms of the disease — a highly aggressive one that seems to evade the urine test, and a more insidious form that is readily detected but frequently regresses of its own accord.

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References and links

ORIGINAL RESEARCH PAPER Woods, W. G. *et al.* Screening of infants and mortality due to neuroblastoma. *N. Engl. J. Med.* **346**, 1041–1046 (2002) | Schilling, F. H. *et al.* Neuroblastoma screening at one year of age. *N. Engl. J. Med.* **346**, 1041–1046 (2002)