Behold *BRCA2*!

Last December, the race to unearth the second hereditary breast and ovarian cancer gene, *BRCA2*, was concluded. Michael Stratton and colleagues reported that they had identified part of the massive *BRCA2* gene on chromosome 13 and identified six mutations in families with breast and ovarian cancer, including some cases of male breast cancer (*Nature* **378**, 789-781; 1995). Not to be outdone, however, scientists at Myriad Genetics, who had isolated *BRCA1* in 1994, rushed to submit a patent application for *BRCA2* coinciding with the publication of the *Nature* paper. In remarkably little time, the group and its collaborators had managed — with the help of the 900 kilobases of publicly available genomic DNA sequence — to assemble the complete gene sequence (GenBank accession number U43746). The fruits of that endeavour are presented by Tavtigian *et al.* on page 333, together with the first results of a mutational analysis for the entire coding region.

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MPIGSKERPTFFEIFKTRCNKADLGPISLNWFEELSSEAPPYNSEPAEESEHKNNNYEPN     60
LFKTPQRKPSYNQLASTPIIFKEQGLTLPLYQSPVKELDKFKLDLGRNVPNSRHKSLRTV    120
KTKMDQADDVSCPLLNSCLSESPVVLQCTHVTPQRDKSVVCGSLFHTPKFVKGRQTPKHI    180
SESLGAEVDPDMSWSSSLATPPTLSSTVLIVRNEEASETVFPHDTTANVKSYFSNHDESL    240
KKNDRFIASVTDSENTNQREAASHGFGKTSGNSFKVNSCKDHIGKSMPNVLEDEVYETVV    300
DTSEEDSFSLCFSKCRTKNLQKVRTSKTRKKIFHEANADECEKSKNQVKEKYSFVSEVEP    360
NDTDPLDSNVAHQKPFESGSDKISKEVVPSLACEWSQLTLSGLNGAQMEKIPLLHISSCD    420
QNISEKDLLDTENKRKKDFLTSENSLPRISSLPKSEKPLNEETVVNKRDEEQHLESHTDC    480
ILAVKQAISGTSPVASSFQGIKKSIFRIRESPKETFNASFSGHMTDPNFKKETEASESGL    540
EIHTVCSQKEDSLCPNLIDNGSWPATTTQNSVALKNAGLISTLKKKTNKFIYAIHDETFY    600
KGKKIPKDQKSELINCSAQFEANAFEAPLTFANADSGLLHSSVKRSCSQNDSEEPTLSLT    660
SSFGTILRKCSRNETCSNNTVISQDLDYKEAKCNKEKLQLFITPEADSLSCLQEGQCEND    720
PKSKKVSDIKEEVLAAACHPVQHSKVEYSDTDFQSQKSLLYDHENASTLILTPTSKDVLS    780
NLVMISRGKESYKMSDKLKGNNYESDVELTKNIPMEKNQDVCALNENYKNVELLPPEKYM    840
RVASPSRKVQFNQNTNLRVIQKNQEETTSISKITVNPDSEELFSDNENNFVFQVANERNN    900
LALGNTKELHETDLTCVNEPIFKNSTMVLYGDTGDKQATQVSIKKDLVYVLAEENKNSVK    960
QHIKMTLGQDLKSDISLNIDKIPEKNNDYMNKWAGLLGPISNHSFGGSFRTASNKEIKLS   1020
EHNIKKSKMFFKDIEEQYPTSLACVEIVNTLALDNQKKLSKPQSINTVSAHLQSSVVVSD   1080
CKNSHITPQMLFSKQDFNSNHNLTPSQKAEITELSTILEESGSQFEFTQFRKPSYILQKS   1140
TFEVPENQMTILKTTSEECRDADLHVIMNAPSIGQVDSSKQFEGTVEIKRKFAGLLKNDC   1200
NKSASGYLTDENEVGFRGFYSAHGTKLNVSTEALQKAVKLFSDIENISEETSAEVHPISL   1260
SSSKCHDSVVSMFKIENHNDKTVSEKNNKCQLILQNNIEMTTGTFVEEITENYKRNTENE   1320
DNKYTAASRNSHNLEFDGSDSSKNDTVCIHKDETDLLFTDQHNICLKLSGQFMKEGNTQI   1380
KEDLSDLTFLEVAKAQEACHGNTSNKEQLTATKTEQNIKDFETSDTFFQTASGKNISVAK   1440
ESFNKIVNFFDQKPEELHNFSLNSELHSDIRKNKMDILSYEETDIVKHKILKESVPVGTG   1500
NQLVTFQGQPERDEKIKEPTLLGFHTASGKKVKIAKESLDKVKNLFDEKEQGTSEITSFS   1560
HQWAKTLKYREACKDLELACETIEITAAPKCKEMQNSLNNDKNLVSIETVVPPKLLSDNL   1620
CRQTENLKTSKSIFLKVKVHENVEKETAKSPATCYTNQSPYSVIENSALAFYTSCSRKTS   1680
VSQTSLLEAKKWLREGIFDGQPERINTADYVGNYLYENNSNSTIAENDKNHLSEKQDTYL   1740
SNSSMSNSYSYHSDEVYNDSGYLSKNKLDSGIEPVLKNVEDQKNTSFSKVISNVKDANAY   1800
PQTVNEDICVEELVTSSSPCKNKNAAIKLSISNSNNFEVGPPAFRIASGKIVCVSHETIK   1860
KVKDIFTDSFSKVIKENNENKSKICQTKIMAGCYEALDDSEDILHNSLDNDECSTHSHKV   1920
FADIQSEEILQHNQNMSGLEKVSKISPCDVSLETSDICKCSIGKLHKSVSSANTCGIFST   1980
ASGKSVQVSDASLQNARQVFSEIEDSTKQVFSKVLFKSNEHSDQLTREENTAIRTPEHLI   2040
SQKGFSYNVVNSSAFSGFSTASGKQVSILESSLHKVKGVLEEFDLIRTEHSLHYSPTSRQ   2100
NVSKILPRVDKRNPEHCVNSEMEKTCSKEFKLSNNLNVEGGSSENNHSIKVSPYLSQFQQ   2160
DKQQLVLGTKVSLVENIHVLGKEQASPKNVKMEIGKTETFSDVPVKTNIEVCSTYSKDSE   2220
NYFETEAVEIAKAFMEDDELTDSKLPSHATHSLFTCPENEEMVLSNSRIGKRRGEPLILV   2280
GEPSIKRNLLNEFDRIIENQEKSLKASKSTPDGTIKDRRLFMHHVSLEPITCVPFRTTKE   2340
RQEIQNPNFTAPGQEFLSKSHLYEHLTLEKSSSNLAVSGHPFYQVSATRNEKMRHLITTG   2400
RPTKVFVPPFKTKSHFHRVEQCVRNINLEENRQKQNIDGHGSDDSKNKINDNEIHQFNKN   2460
NSNQAAAVTFTKCEEEPLDLITSLQNARDIQDMRIKKKQRQRVFPQPGSLYLAKTSTLPR   2520
ISLKAAVGGQVPSACSHKQLYTYGVSKHCIKINSKNAESFQFHTEDYFGKESLWTGKGIQ   2580
LADGGWLIPSNDGKAGKEEFYRALCDTPGVDPKLISRIWVYNHYRWIIWKLAAMECAFPK   2640
EFANRCLSPERVLLQLKYRYDTEIDRSRRSAIKKIMERDDTAAKTLVLCVSDIISLSANI   2700
SETSSNKTSSADTQKVAIIELTDGWYAVKAQLDPPLLAVLKNGRLTVGQKIILHGAELVG   2760
SPDACTPLEAPESLMLKISANSTRPARWYTKLGFFPDPRPFPLPLSSLFSDGGNVGCVDV   2820
IIQRAYPIQWMEKTSSGLYIFRNEREEEKEAAKYVEAQQKRLEALFTKIQEEFEEHEENT   2880
TKPYLPSRALTRQQVRALQDGAELYEAVKNAADPAYLEGYFSEEQLRALNNHRQMLNDKK   2940
QAQIQLEIRKAMESAEQKEQGLSRDVTTVWKLRIVSYSKKEKDSVILSIWRPSSDLYSLL   3000
TEGKRYRIYHLATSKSKSKSERANIQLAATKKTQYQQLPVSDEILFQIYQPREPLHFSKF   3060
LDPDFQPSCSEVDLIGFVVSVVKKTGLAPFVYLSDECYNLLAIKFWIDLNEDIIKPHMLI   3120
AASNLQWRPESKSGLLTLFAGDFSVFSASPKEGHFQETFNKMKNTVENIDILCNEAENKL   3180
MHILHANDPKWSTPTKDCTSGPYTAQIIPGTGNKLLMSSPNCEIYYQSPLSLCMAKRKSV   3240
STPVSAQMTSKSCKGEKEIDDQKNCKKRRALDFLSRLPLPPPVSPICTFVSPAAQKAFQP   3300
PRSCGTKYETPIKKKELNSPQMTPFKKFNEISLLESNSIADEELALINTQALLSGSTGEK   3360
QFISVSESTRTAPTSSEDYLRLKRRCTTSLIKEQESSQASTEECEKNKQDTITTKKYI    3418
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The BRCA2 protein: the putative granin sequence is underlined. The weak region of homology between BRCA1 and BRCA2 noted by Stratton *et al.* begins at lysine 2064 and extends for 80 residues.

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If *BRCA1* was a large gene, then *BRCA2* is gargantuan. The gene encodes a protein of 3,418 amino acids (Stratton *et al.* presented about 68% of the coding sequence in their paper). And while *BRCA2* certainly contains some general similarities to *BRCA1*, Tavtigian *et al.* report that *BRCA2* shows no significant homologies with *BRCA1* or anything else in the database for that matter. However, results presented on page 298 of this issue by the teams of Jeffrey Holt and Roy Jensen at Vanderbilt University, and Mary-Claire King at the University of Washington in Seattle, suggest that there may be a significant motif in both *BRCA1 and BRCA2*. The sequence in question is the granin consensus site (see *News & Views* on page 223), which is located in the middle of BRCA1 but in the more orthodox C-terminal region of BRCA2. It should be stressed that no functional studies have yet been performed on BRCA2, and indeed the evidence for BRCA1 acting as a granin is largely circumstantial at this stage.

The Myriad group has also uncovered nine separate mutations in different families, out of a total of 18 tested which were thought likely to be attributable to a flaw in *BRCA2*. The results are both good and bad from the perspective of genetic testing. The bad news is that each of the 15 mutations published so far are distinct, apparently thwarting those who had hoped that genetic predisposition at this locus might be confined to a small number of defects. However, virtually all of the mutations witnessed so far are nonsense or frameshift mutations, which might simplify the task of genetic testing. Who will reap the rewards from such tests is another question entirely. Two rival patent applications have been submitted in the United Kingdom and United States. Each group obviously feels it has a case: the European group was the first to publish evidence that *BRCA2* had been cloned, by virtue of documenting a handful of mutations in affected families. By contrast, the Myriad team points to having been the first to compile the full-length sequence of the gene. Even as the process of evaluating these claims begins, there is the possibility that the two teams will reach some form of cross-licensing agreement.