A large multisite cancer family is linked to BRCA2

P Tonin, P Ghadirian, C Phelan, G M Lenoir, H T Lynch, F Letendre, D Belanger, M Monté, S A Narod

Abstract
We identified a large French-Canadian family with 21 cases of breast cancer, including two affected brothers. Segregation of markers from chromosome 13q in this family showed linkage to the BRCA2 gene locus (lod=3.67 at D13S289). A number of cancers of other types occurred in this family, including three cases of prostate cancer and two cases of lymphoma. The penetrance of breast cancer among BRCA2 carriers is estimated to be 75% to the age of 70.

Results
The majority of families with a dominant predisposition to breast cancer may be attributed to mutations in either the BRCA1 gene on chromosome 17 or the BRCA2 gene on chromosome 13q. The BRCA1 gene was cloned in 1994 and predictive testing by direct mutation analysis is now available. BRCA1 accounts for the majority of families with the breast-ovarian cancer syndrome, but few families with cases of male breast cancer are linked to this gene. A second breast cancer locus, BRCA2, was mapped to chromosome 13q in 1994. The mapping of the BRCA2 gene was achieved by the application of a genomic search process to 15 extended families with multiple cases of breast cancer which had previously been shown not to be linked to the BRCA1 locus. Cases of male breast cancer appeared in six of the 15 families. BRCA2 mapped to the interval between D13S289 and D13S267, close to the marker D13S260. Overall, it was estimated that 74% of the 15 families were linked to BRCA2 and five of six families with male breast cancer gave positive lod scores to markers in the region. In order to confirm the association of hereditary male breast cancer and the BRCA2 locus, and to characterise further the range of cancers associated with this gene, we have typed a large French-Canadian cancer family with six polymorphic markers from chromosome 13q.

Materials and methods
This family was identified in the course of a case-control study of familial risk factors in cancer conducted at the Hotel Dieu Hospital in Montreal. Blood for DNA analysis was obtained from 58 people. Lymphocyte DNA was typed with six highly polymorphic CA repeat probes from chromosome 13q: AFM238z, D13S290, D13S289, D13S260, D13S267, and D13S267. BRCA2 is located between D17S289 and D17S267. The relative position of BRCA2 and D17S260 is not yet known. Lod scores were calculated using the LINKAGE program. Breast cancer susceptibility was modelled as an autosomal dominant trait with incomplete penetrance. Men with breast cancer were assumed to be carriers of the BRCA2 mutation. Cancers at sites other than the breast were not used to define the individual phenotypes. The six CA repeat loci were analysed as systems of nine equally frequent alleles.
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were not confirmed; liver cancer in subject 193 and leukaemia in subject 214. One of the two patients with lymphoma, as well as the patients with leukaemia, liver cancer, colon cancer, and laryngeal cancer appear to be carriers of the BRCA2 gene mutation; the genetic status for the other three cancer cases is not known. The two cases of breast cancer appear to be the only cases identified among non-carriers (sporadic cancers) in this family.

Discussion
This large French-Canadian kindred confirms the assignment of a breast cancer susceptibility gene to chromosome 13q, as reported by Wooster et al\(^4\) in 1994. Male breast cancer is a characteristic of about one-half of the BRCA2 linked families reported to date. Our family is unusual because of the marriage between subjects 60 and 61, both of whom have had breast cancer, and who appear to have inherited the same BRCA2 mutation from a common great-grandparent. All three of their daughters have had early onset breast cancer, although none is homozygous for the BRCA2 mutation.

We also follow a second, large, site specific breast cancer family (IARC family 2932) which was included in the original report of Wooster et al.\(^4\) The lod score for linkage of family 2932 to the D13S267 marker was 2.05. Family 2932 contains 13 cases of invasive breast cancer (mean age 45-7 years) as well as two cases of lung cancer, two of testicular cancer, and single cases each of stomach, prostate, brain, melanoma, and non-melanoma skin cancer. There are no male breast cancers in this family. A case of seminoma occurred in a 55 year old BRCA2 carrier. The other testicular cancer (embryonal cell carcinoma at the age of 22) was in a non-carrier. In the two families combined, the penetrance of breast cancer was 42\% by age 50 and 75\% by age 70. Although a moderately increased risk of ovarian cancer has been reported in BRCA2 carriers,\(^4\) none of the 48 BRCA2 carriers in either of the two pedigrees is affected with ovarian cancer.

It appears that many of the BRCA1 mutations in Canada are recurrent and are the result of common ancestors.\(^7\) It is likely that the frequencies of mutant alleles of BRCA1 and BRCA2 (and the ratios of BRCA1 to BRCA2 linked families) will differ between ethnic groups. This is the first reported example of a BRCA2 linked French-Canadian family; it is not yet clear if this is the predominant form of hereditary breast cancer in this population. It will be important to establish the relative contributions of BRCA1 and BRCA2 to hereditary cancer in different ethnic populations if predictive testing programmes are to operate efficiently.

This work was supported by the Department of the Army grants, DAMD17-94-J-4299, the Fonds de la Recherche en Santé du Quebec (FRSQ), and the Canadian Genetics Diseases Network. We thank France Dion, Kenneth Morgan, Chantal Perret, Deborah Lambert, and Jean Latreille for technical expertise and helpful discussions.

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doi: 10.1136/jmg.32.12.982

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