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INVITED EDITORIAL
Population Genetics of BRCA1 and BRCA2

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In 1992, the Musée de L'Homme in Paris presented a natural history exhibit entitled "Tous Parents, Tous Différents," a beautiful scientific and artistic exploration of human evolution and biological variation. The themes of that exhibit were that present-day human diversity is the consequence of the interaction of genetic change (mutation), adaptation to climate and to disease (selection), social instability and individual autonomy (leading to migration), and marriage patterns (population structure). The population genetics of inherited variation in BRCA1 and BRCA2, as presented in this issue of the *Journal* and in other recent publications, illustrates the same principles (for references, see table 1). BRCA1 and BRCA2 have each undergone multiple mutations; the resultant alleles have migrated with the peoples in which they occur; and disease-associated mutations have persisted, no doubt because of late onset of disease and, hence, little or no deleterious impact of mutant alleles on genetic fitness.

This issue of the *Journal* includes analyses of inherited mutations in BRCA1 and/or BRCA2 in high-risk families from nine regions: Finland, France, Holland and Belgium, Hungary, Iceland, Israel, Russia, Sweden and Denmark, and the United States. Previous reports also presented information from these regions, as well as from Britain, Canada, Germany, Italy, Norway, and Japan. In their individual studies, authors addressed some or all of the following questions: What proportion of high-risk families have mutations in BRCA1? in BRCA2? What mutations appear in multiple families, either from the same region or elsewhere? How far have alleles migrated? How do shared mutations reflect population structure? How frequent are ancient mutations in the populations in which they arose? What risks (penetrances) are associated with shared mutations? For this commentary, we have integrated the data from all groups and have performed some simple comparisons.

Frequencies of BRCA1 and BRCA2 mutations in high-risk families and in other series of patients from all populations represented thus far in the literature are indicated in table 1. For some populations (e.g., Britain, the United States, and France), combined data from multiple studies are presented by ascertainment scheme. For this combined analysis, families at "high risk" of breast and/or ovarian cancer are defined as those with either at least three female relatives with breast cancer or at least two affected relatives if one case is either ovarian cancer or male breast cancer. With the exception of the Israeli studies, individuals or families were included in this table only if the entire BRCA1 and/or BRCA2 sequence was evaluated, in order to generate unbiased estimates of relative frequencies of alleles. The integrated data suggest several conclusions.

First, the proportion of high-risk families with breast or ovarian cancer attributable to BRCA1 mutations varies widely among populations. BRCA1 mutations are by far the most common in Russia (occurring in 79% of breast/ovarian cancer families), where most mutation-carrying families have one of two common alleles. Interestingly, the most common allele in Russia, 5382insC, is also the most common among Europeans as a whole and has migrated far from the Baltic area where it probably originated. In contrast, the second most common allele in Russia, 4153delA, has not been observed outside Russia so far. The proportion of familial breast and ovarian cancer that results from BRCA1 mutations is next highest in Israel (occurring in 47% of high-risk families) and Italy (29% of families), although the population dynamics of BRCA1 in these two populations are distinctly different. Two BRCA1 mutations explain the observed BRCA1 Jewish families in Israel (where only ancient mutations were genotyped), whereas nearly all BRCA1 mutations in Italian families are unique. Clearly, the frequency of families with BRCA1 mutations is not highly correlated with the number of different mutations, because individual mutations may be common or rare. If it is assumed that the BRCA1 gene has the same underlying mutation rate in all parts of the world, then the phenomenon of many unique mutations in Italy, versus two ancient, common mutations in Israel, likely reflects the small number of founders in the current Jewish population, compared with the many founders in modern Italy. Between 20% and 25% of high-risk families in Britain, France, Scandinavia, and Hungary have

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Table 1

Breast and Ovarian Cancer Families and Patients from Various Populations Tested for Inherited Mutations in BRCA1 and BRCA2 and Patients

Population	No. of Families or Patients with Mutations/No. of Families or Patients Screened		Reference(s)
	BRCA1	BRCA2	
Families with three or more cases of female breast and/or ovarian cancer:			
Britain	71/339 (21%)	25/290 (9%)	Gayther et al. (1995, 1996, 1997*b*); Xu et al. (1997)
Canada	12/30 (40%)	8/49 (16%)	Simard et al. (1994); Phelan et al. (1996)
Finland		8/100 (8%)	Vehmanen et al. (1997)
France	38/160 (24%)	14/77 (18%)	Serova-Sinilnikova et al. (1997); Stoppa-Lyonnet et al. (1997)
Germany	9/49 (18%)		Jandrig et al. (1996); Hamann et al. (1997)
Holland and Belgium	71/517 (14%)		Hogervorst et al. (1995); Peelen et al. (1997)
Hungary	7/32 (22%)	4/32 (13%)	Ramus et al. (1997)
Iceland	1/11 (9%)	7/11 (64%)	Thorlacius et al. (1996)
Israel	16/34 (47%)	8/34 (24%)	Levy-Lahad et al. (1997)
Italy	21/73 (29%)		Caligo et al. (1996); Montagna et al. (1996); De Benedetti et al. (1996)
Japan	2/20 (10%)		Inoue et al. (1995)
Norway	3/25 (12%)		Andersen et al. (1996)
Russia	15/19 (79%)		Gayther et al. (1997*a*)
Sweden and Denmark	24/106 (23%)	12/106 (11%)	Johannsson et al. (1996); Håkansson et al. (1997)
United States	69/179 (39%)	24/94 (25%)	Castilla et al. (1994); Friedman et al. (1994, 1995); Struewing et al. (1995); Arena et al. (1996); Couch et al. (1996); Serova et al. (1996, 1997); Tavtigian et al. (1996); Gao et al. (1997); Schubert et al. (1997)
Families with male and female breast cancer:			
United States	2/24 (8%)	12/64 (19%)	Couch et al. (1996); Friedman et al. (1997); Serova et al. (1997)
Hungary	0/6 (0%)	2/6 (33%)	Ramus et al. (1997)
Iceland	0/10 (0%)	9/10 (90%)	Thorlacius et al. (1996)
Breast and/or ovarian cancer patients not selected for family history:			
Iceland		42/497 (8%)	Johannesdottir et al. (1996)
Italy	4/49 (8%)		De Benedetti et al. (1996)
Israel	23/243 (9%)	14/243 (6%)	Abeliovich et al. (1997)
Japan	8/179 (4%)	2/103 (2%)	Matsushima et al. (1995); Katagiri et al. (1996); Miki et al. (1996)

BRCA1 mutations, and, in each region, BRCA1 mutations are substantially more common than BRCA2 mutations. Inherited BRCA1 mutations explain <20% of high-risk families in Holland and Belgium, in Germany, in Norway, and in Japan. The United States and Canada, where high-risk families are exclusively migrants, are intermediate.

Second, in most populations, BRCA1 and BRCA2 together explain 6%–10% of breast and ovarian cancer unselected for family history; in Israel, the attributable fraction is somewhat higher (15%). The first segregation analysis of breast cancer in a large, population-based series of patients predicted that 4%–10% of breast cancer patients unselected for family history would carry inherited predisposing alleles in then-hypothetical BRCA genes (Newman et al. 1988).

Third, ~30% of high-risk families have no detected mutations in either BRCA1 or BRCA2. These include 3 of 4 Hungarian families with at least six cases of breast or ovarian cancer (Ramus et al. 1997 [in this issue]); 2 of 6 male breast cancer families and 15 of 23 female breast cancer families in the series of midwestern American families analyzed by the International Agency for Research on Cancer (Serova et al. 1997); 4 of 25 Swedish families with both breast cancer and at least two cases of ovarian cancer (Håkansson et al. 1997 [in this issue]); and 9 of 48 American families with at least four cases of breast and/or ovarian cancer (Schubert et al. 1997 [in this issue]). These observations led several groups to suggest the existence of other BRCA genes. BRCA2 mutations are more frequent than BRCA1 mutations only in Iceland, which is unique in that one mutation explains virtually all inherited breast and ovarian cancer (Thorlacius et al. 1996). In the populations that founded Iceland, the 999del5 mutation thus far has been observed only in two Finnish breast cancer families (Ander-

sen et al. 1996; Håkansson et al. 1997; Vehmanen et al. 1997 [in this issue]). The preponderance of a single BRCA2 mutation in Iceland represents one of the most dramatic examples of a founder mutation in isolated populations where mutation rate (low), endogamy and isolation (high), and secular trend in penetrance all have contributed to the current population structure (Thorlacius et al. 1997 [in this issue]).

Fourth, in families with male breast cancer, BRCA2 mutations are more common than BRCA1 mutations, as has been apparent since BRCA2 was mapped (Wooster et al. 1994). The combined data from U.S. studies suggest that BRCA2 is responsible for 19% of familial male breast cancer (Couch et al. 1996; Friedman et al. 1997; Serova et al. 1997; table 1) but for a considerably lower fraction of male breast cancer in the general population (Couch et al. 1996; Friedman et al. 1997).

Finally, in all regions other than Iceland, the frequency of BRCA1 mutations is 1.5–2.0-fold higher than the frequency of BRCA2 mutations. Lower prevalence of BRCA2 mutations in families and patients could be due to fewer mutations, to lower penetrance, and/or to later age at onset of BRCA2 breast cancer. Survival analysis adjusted for multiple ascertainment of high-risk families indicates that the lifetime risks of breast cancer associated with BRCA1 and BRCA2 are approximately equal but that the age at onset is later among BRCA2-mutation carriers (Schubert et al. 1997). The difference in BRCA1- versus BRCA2-mutation frequency probably represents a true difference in the relative contribution of these two genes to the hereditary breast/ovarian cancer burden, rather than ascertainment bias: in 53 site-specific breast cancer families ascertained in the United States, the frequency of BRCA1 mutations was twice the frequency of BRCA2 mutations (Friedman et al. 1994, 1995; Serova et al. 1997; Schubert et al. 1997).

Tables 2 and 3 and figure 1 present ancient mutations of BRCA1 and BRCA2 that have been identified in multiple families. The proportion of such BRCA1 and BRCA2 mutations varies widely among populations, ranging from no repeated mutations in Italy to nearly all hereditary breast and ovarian cancer attributable to one or a few mutations in Iceland and Israel. These differences represent historical influences of migration, population structure, and geographic or cultural isolation.

In the Ashkenazim, two ancestral mutations, BRCA1 185delAG and BRCA2 6174delT, each appear in the general population at ~1% frequency; a third mutation, BRCA1 5382insC, occurs at a population frequency of 0.11% (for review, see Roa et al. 1996; Tonin et al. 1996). Although a significant proportion of breast and ovarian cancer in Ashkenazi Jews is attributable to these three ancient mutations (Abeliovich et al. 1997), 163 (52%) of 310 Ashkenazi high-risk breast and/or ovarian cancer families do not carry any of the recurrent mutations (Tonin et al. 1996; Abeliovich et al. 1997; Levy-Lahad et al. 1997 [in this issue]; Schubert et al. 1997). Whether these families carry other, novel BRCA1 or BRCA2 alleles (Schubert et al. 1997), have mutations in other, as-yet-unidentified susceptibility loci, or are high risk for nongenetic reasons remains to be determined.

The age of the 185delAG mutation was estimated at ~46 generations, or 1,000–1,500 years (Neuhausen et al. 1996). However, the appearance of the 185delAG mutation embedded in the same haplotype among Iranian, Iraqi, and Ashkenazi Jewish families suggests that this mutation predates the separation of these communities from each other at the time of the destruction of the Second Temple in year 70 of the common era. This mutation is ≥2,000 years old (Abeliovich et al. 1997; Levy-Lahad et al. 1997).

The 5382insC mutation initially was observed in northern and eastern European families (Simard et al. 1994; Friedman et al. 1995; Shattuck-Eidens et al. 1995; Neuhausen et al. 1996). It has now been observed in Russian (Gayther et al. 1997*a* [in this issue]), Hungarian (Ramus et al. 1997), and Ashkenazi Jewish (Tonin et al. 1996) families. The allele frequency of 5382insC has not yet been determined in either Russia or Hungary; however, both the common founding haplotype in mutation carriers (Simard et al. 1994; Gayther et al. 1997*a*; Ramus et al. 1997) and its high frequency in eastern European populations are consistent with a Baltic origin during the medieval period (~38 generations ago) (Neuhausen et al. 1996).

Most other ancient mutations have more limited geographic and linguistic distributions. The British and French populations share the most alleles, three of which also have been observed in the Dutch, reflecting the extensive historical exchange among these populations. Nevertheless, each of these regions also has population-specific, frequently occurring mutations. Particularly striking is the frequency of country-specific mutations in the Netherlands and in Sweden. Of the 10 multiply ascertained BRCA1 mutations in the Netherlands, 6 (including the by-far-most-common 2803delAA) are not observed elsewhere (Peelen et al. 1997 [in this issue]); of the 5 such BRCA1 mutations in Sweden, the most common 3 have not been observed elsewhere (Johannsson et al. 1996; Håkansson et al. 1997).

Many European mutations have been observed in the United States or Canada, reflecting European migrations to North America. However, the nature of BRCA1 and BRCA2 mutations in Africa is just beginning to be revealed by the evaluation of families of combined African and European or American ancestry (Castilla et al. 1994; Arena et al. 1996; Gao et al. 1997 [in this issue]; Stoppa-Lyonnet et al. 1997 [in this issue]). In 22 African-American and African-French families, eight novel BRCA1 mutations have been identified. Three mutations occurred in two families each, but no mutations occurred

Table 2

Ancient BRCA1 Mutations in Breast and Ovarian Cancer Families and Patients

Exon	BRCA1 Nucleotide Change	No. of Mutations													
		Britain	France	Holland and Belgium	Germany	Norway	Sweden and Denmark	Italy	Austria	Hungary	Russia	Israel	Japan	United States	Canada
11	1294del40	4												2	1
2	185delAG (York)	3													
20	5382insC	2	5	2	1			1		4	9	12		4	4
11	4184del4	6	3											2	1
11	3875del4	4	1	1							1			1	
13	4446C→T	3	2											2	
11	3452del4	2	1												
11	1136insA	1		1		3									1
11	3600del11		3											2	
I-5	332(−11)T→G		1											2	
2	185delAG (Jewish)		4	5	1					2		27		10	4
11	2803delAA			19											
11	2312del5			7											
11	1411insT			5											
11	2457C→T			4										1	
11	3604delA			4											
11	2841G→T			3										1	
11	1499insA							5							
11	1675delA					5[a]	1								
11	2594delC						7								
11	3166ins5						4								
11	1806C→T						3								
5	Cys61Gly				1		1		3[a]					4	
11	2795del4								3						
11	4153delA										3				
5	307T→A												2		
5	Cys64Gly													2	
11	2800delAA[b]													2	
	Others	21	32	21	6	0	11	19	1[a]	1	3	Not tested	8	30	1

[a] From Breast Cancer Information Core (1997).
[b] A Scots breast cancer patient is homozygous for this mutation (Boyd et al. 1996).

Table 3

Ancient BRCA2 Mutations in Breast and Ovarian Cancer Families and Patients

Exon	BRCA2 Nucleotide Change	No. of Mutations								
		Britain	France	Hungary	Sweden and Denmark	Finland	Iceland	Israel	United States	Canada
11	6503delTT	5								
11	5573del/insA/AA	2	1							
11	3034del4	3	1						1	2
10	1529del4	1							1	
10	2034insA	1							1	
11	6174delT	1		1				11	5	1
2	277delAC			1					1	
23	9326insA		1	1	1					
11	4486delG				2					
9	999del5					2	61			
18	8555T→G					2				
I-23	9346(−2)A→G					2				
9	982del4								3	
20	8764delAG									2
	Other	12	13	3	10	2	0	Not tested	19	3

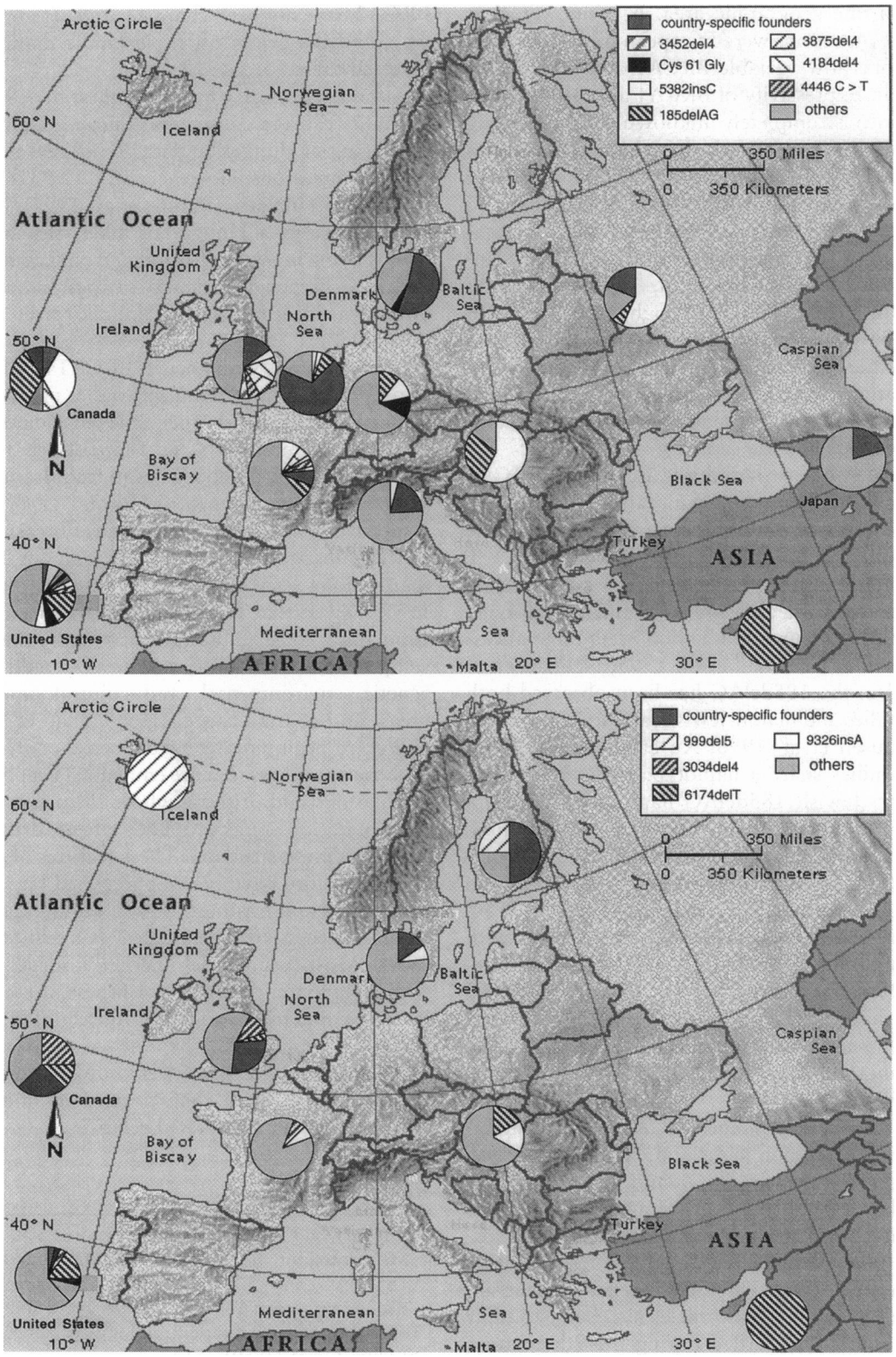

Figure 1 Population distributions of ancient BRCA1 and BRCA2 mutations. The proportions of founder, population-specific, and novel mutations are depicted, by country, for (*A*) BRCA1 and (*B*) BRCA2. With the exception of Israel, data is shown only if the entire BRCA1 and/or BRCA2 sequence was evaluated. Specific mutations identified in two or more countries other than the United States or Canada are highlighted. "Country-specific founders" refers to mutations identified in two or more unrelated families within a country, but not reported elsewhere in Europe; and "others" refers to novel mutations. Unspecified color designations in the United States and Canada reflect mutations that are identical to country-specific founders identified in Europe.

in more than one geographic area. It is not yet clear whether these mutations were European or African originally, let alone how variable BRCA1 and BRCA2 are in Africa itself. Expressivity of BRCA1 and BRCA2 mutations in Africa is completely unknown. Understanding the outcomes associated with inherited BRCA1 and BRCA2 mutations in Africa could help illuminate both the biology of these genes and nongenetic influences on penetrance of mutant alleles. BRCA1 and BRCA2 mutations observed in Japan are unique to that country (Inoue et al. 1995; Matsushima et al. 1995; Katagiri et al. 1996; Miki et al. 1996), although no other Asian populations have been screened yet. It will be fascinating to learn whether the same pattern of some widely migrating mutations and other population-specific mutations appears in Asia as in Europe and whether mutant alleles are expressed as the same forms of cancer.

Although the majority of multiply ascertained BRCA1 alleles appear to represent single mutation events, there are at least three instances of independent origins of the same mutation. The 4184del4 frameshift and 4446C→T nonsense mutations have each been observed on two distinct haplotypes, in addition to a third haplotype, which may represent a recombination event of an ancestral chromosome (Friedman et al. 1995; Neuhausen et al. 1996). Also, the 185delAG has been observed both in Jewish families and in non-Jewish families from Yorkshire (Neuhausen et al. 1996; Xu et al. 1997). Three Yorkshire families share a haplotype that differs from the Ashkenazi Jewish 185delAG haplotype (Xu et al. 1997), indicating independent origins of the mutation.

Although BRCA2 has been less fully studied, population-specific founder mutations are beginning to emerge. Finnish families with the nonsense mutation T8555G share an ~14-cM region of BRCA2, and families with the splice mutation A9346(−2)G share an ~1-cM region of BRCA2. British families with BRCA2 6503delTT share intragenic polymorphisms (Mazoyer et al. 1996), and Swedish families with the BRCA2 4486delG mutation share the D13S171 allele (Håkansson et al. 1997).

However, the history of the BRCA2 999del5 mutation, which is so common in Iceland, is still mysterious. This mutation also appears in Finland, but the Finnish haplotype shares only common intragenic BRCA2 alleles with the 600-kb Icelandic haplotype (Gudmundsson et al. 1996; Vehmanen et al. 1997). The mutation may have migrated from Finland to Iceland during ancient times, or identity at these alleles may be due simply to chance. Iceland was settled during the 9th century, according to tradition, by western Norwegians. Principal-component analysis of genetic distances among European populations indicates that Icelanders are closest to Norwegians, then to the English, Belgians, and Danes (Cavalli-Sforza et al. 1994). Finns are considerably more distantly related to these populations. BRCA1 and BRCA2 have not been characterized yet in western Norway, and the origin of the Icelandic mutation may be revealed there.

Although Hungary has the highest male breast cancer mortality rates in continental Europe (La Vecchia et al. 1992), initial Hungarian data do not reveal any founder BRCA2 mutations. However, BRCA2 9326insA, identified first in Hungary (Ramus et al. 1997), has been observed since in a Hungarian male with breast cancer who is living in Sweden (Borg, personal communication) and in a French breast and ovarian cancer family of unknown ancestry (Serova-Sinilnikova et al. 1997 [in this issue]).

In populations with ancient BRCA1 or BRCA2 mutations, genetic epidemiological studies may identify environmental causes and other genes that modify inherited risk. For example, BRCA1 185delAG is found at approximately equal frequencies in Iraqi/Iranian and Ashkenazi Jewish families (at 0.5% and 1.0% frequencies, respectively: Modan et al. 1996), yet breast and ovarian cancer rates are significantly lower among Iraqi/Iranian than among Ashkenazi Jewish women (Steinitz et al. 1989). Given that BRCA1 185delAG itself is constant, comparing those mutation-carrying women who develop disease with those who do not could reveal other genetic, environmental, and cultural contributors to breast and ovarian cancer (Levy-Lahad et al. 1997).

We are beginning to have a sense of the proportion of those mutations that are embedded deeply in different populations and of those whose history is shorter. Ancient mutations reflect founder effects, drift, migration, and population structure. These features of gene geography heretofore have been appreciated largely for polymorphisms and for mutations in genes expressed as autosomal recessive phenotypes (Cavalli-Sforza et al. 1994). Most dominantly inherited disorders, even those with no apparent decrease in fitness, are characterized by many mutations and by a measurable rate of new germ-line mutations. The rate of such mutations in BRCA1 and BRCA2 is not yet known, primarily because current studies have characterized mutations in large families with many affected relatives.

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