Commentary

Founder populations and their uses for breast cancer genetics

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Abstract

Numerous founder mutations have been reported in *BRCA1* and *BRCA2.* For genetic screening of a population with a founder mutation, testing can be targeted to the mutation, allowing for a more rapid and less expensive test. In addition, more precise estimates of the prior probability of carrying a mutation and of the likelihood of a mutation carrier developing cancer should be possible. For a given founder mutation a large number of carriers are available, so that focused scientific studies of penetrance, expression, and genetic and environmental modifiers of risk can be performed. Finally, founder populations may be a powerful resource to localize additional breast cancer susceptibility loci, because of the reduction in locus heterogeneity.

Keywords: *BRCA1*, *BRCA2*, breast cancer genes, founder mutations, genetic epidemiology

Introduction

Ethnic differences in the prevalences of many diseases have been observed. For example, sickle-cell anemia in individuals of African descent, Tay–Sachs disease in Ashkenazi Jews [1], and approximately 30 diseases in Finland [2] are more prevalent than in other populations. A likely reason for a preponderance of a disease in a specific population is a founder effect. Founder effects occur when a population is established by a small number of people or when a bottleneck occurs that reduces the population to a small number. When population expansion occurs, the mutation in a founder becomes prevalent in a larger proportion of the population. There may also be a selective advantage to the mutation carrier. By following genetic relationships over many generations, the significance of founder effects can be studied. Diamond and Rotter [3] reviewed studies of the Afrikaner population of South Africa. In 1652, one founding immigrant carried a gene for Huntington's chorea and one brother–sister pair carried a gene for lipoid proteinosis. The result of founder effects is that these diseases are more common in South Africa than in Holland from where the carriers emigrated.

Founder populations can be useful in genetic studies, particularly for genetic mapping of complex traits. There is little genetic heterogeneity, so that the majority of individuals with disease will carry the same gene mutation. Linkage disequilibrium between the site of the gene and close markers will exist, so that shared regions of the genome cosegregating with disease can be more readily discerned. As an example, Hirschprung's disease has been described in individuals of many different backgrounds. Using a Mennonite population, in which all affected individuals could be traced to a single common ancestral couple, one of the genes for the disease was localized and subsequently identified [4].

Once founder mutations are identified, researchers are able to examine prevalence of mutations in different populations and mutation-specific effects on penetrance and

disease phenotype. Possibly, better estimates of risk for individuals in populations with founder mutations can be calculated. This editorial focuses on founder populations in genetic studies of breast cancer.

Prevalence of mutations in *BRCA1* and *BRCA2*

BRCA1 and *BRCA2*, two genes predisposing to breast and ovarian cancers, were isolated in 1994 and 1995, respectively [5,6]. Since that time, researchers have been screening for mutations in high-risk breast and/or ovarian cancer families and in population-based samples of women with these cancers to determine the prevalence and range of mutations. Over 1300 distinct variants have been found across all population groups, of which approximately 700 are identified as causal [7,8]. A number of these mutations have been identified multiple times [8]. Many of these common mutations have been classified as founder mutations on the basis of a shared haplotype in the genomic region containing the gene. Founder mutations for *BRCA1* and *BRCA2* have been described in numerous populations (Table 1), as well as across populations. For example, *BRCA1* 5382insC has been reported in individuals of Jewish, Dutch, Lithuanian, Russian, Hungarian, Germanic, French, Italian, British, and French–Canadian ancestry [8]. This suggests that this is a relatively old mutation that has spread through migration.

Relative ages of several founder mutations have been investigated by examining the distance over which haplotypes are conserved [9,10]. Based on the general age of a mutation and historic data on migration and social patterns, the origin and subsequent migration of specific mutations may be described. Now that a large number of mutation carriers have been identified the Breast Cancer Linkage Consortium is undertaking such a study for a set of founder mutations.

Table 1

Examples of *BRCA1* and *BRCA2* founder mutations

Population	Mutation	Reference
African–Americans	*BRCA1* 943ins10	[40,41]
	BRCA1 M1775R	
Ashkenazi Jews	*BRCA1* 185delAG *BRCA1* 5382insC *BRCA2* 6174delT	[31,34,38]
Belgians	*BRCA1* IVS5 +3A>G	[42]
Dutch	*BRCA1* 2804delAA	[17,43]
	BRCA1 IVS 21-36del510	
	BRCA1 IVS 12-1643 del3835	
	BRCA2 5573insA	
Finns	*BRCA1* 3745delT	[27]
	BRCA1 IVS 11-2 A>G	
	BRCA2 999del5	
	BRCA2 IVS23-2A>G	
French–Canadians	*BRCA1* R1443X *BRCA2* 8765delAG	[39,44]
Germans	*BRCA1* 5382insC	[45]
	BRCA1 C61G	
Icelanders	*BRCA2* 999del5	[28]
Latvians	*BRCA1* C61G	[46]
	BRCA1 5382insC	
	BRCA1 4153delA	
Norwegians	*BRCA1* 1675delA	[47–49]
	BRCA1 1135insA	
Russians	*BRCA1* 5382insC	[50]
	BRCA1 4153delA	
Swedes	*BRCA1* Q563X	[51]
	BRCA1 3166ins5	
	BRCA1 1201del11	
	BRCA1 2594delC	
	BRCA2 4486delG	

Assessment of risk

Genetic screening

Since the isolation of *BRCA1* and *BRCA2*, genetic testing for mutations is becoming more common in clinical genetic practice. Important considerations are who should be offered predictive testing and when it should be done. In general, mutations in *BRCA1* and *BRCA2* are rare, probably accounting for less than 5% of breast cancers and 10% of ovarian cancers in the population [11,12]. The frequency of *BRCA1* and *BRCA2* mutation carriers in women with breast and/or ovarian cancer is dependent on the study population, and is highest in young women with breast cancer who have a strong family history of breast and/or ovarian cancers. An essential issue for testing is the probability that an individual, with breast or ovarian cancer or with a family history of cancer, will carry a mutation in *BRCA1* or *BRCA2.* Probability models have been developed to predict the likelihood of being a mutation carrier before testing [13–16]. Prior probabilities vary depending on the model used.

For genetic testing, there are several advantages to knowing the founder mutation(s) in a population. First, a more accurate estimate of the prior probability of carrying a mutation should be possible. Second, for mutation detection, testing can be targeted to the founder mutation, allowing for a more rapid and less expensive test. Third, most of the mutation detection techniques are unable to detect large deletions and insertions, so that these types of mutations, which may account for 5–15% of deleterious mutations, would be undetected. If one of these mutations is

known in the population, however, a technique that detects it can be used for mutation screening. For instance, there are two large deletion founder mutations in the Dutch that would not be detectable with standard techniques [17].

Age-specific penetrance

Once an unaffected mutation carrier is identified, the question becomes what is the likelihood that she will develop cancer by a given age (age-specific penetrance). It is especially difficult to answer, because not all factors that contribute to the development of cancer are known. A proportion of individuals who carry mutations will not develop breast cancer or any other cancer. On the basis of estimates from population-based studies of women aged 40 years or younger to estimates from high-incidence breast cancer families of Northern European descent, the cumulative risk of breast cancer by age 70 years for *BRCA1* and *BRCA2* mutation carriers is between 40 and 80% [18–20]. Mutation-specific differences may also be important. There are regions in *BRCA1* and *BRCA2* in which mutations confer higher risks for developing ovarian cancer: 5′ of codon 1435 in exon 13 of *BRCA1* [21] and a 3.3 kilobase region of exon 11 in *BRCA2* (denoted the Ovarian Cancer Cluster Region) [22]. It is unclear whether the differences in risk for ovarian cancer are due to a difference in penetrance of the mutations for breast cancer or ovarian cancer, or both. For *BRCA2*, it has been suggested that the breast cancer risk remains the same, but that the ovarian cancer risk increases [20]. Expression is also variable [23]. In a population with a defined founder mutation(s), more accurate assessment of the likelihood of developing cancer for a mutation carrier should be possible.

Founder mutations

BRCA1 and *BRCA2*

An example of a recurrent, founder mutation is the *BRCA2* 999del5 mutation in the Icelandic population. No other *BRCA2* mutations have been reported in this population. The 999del5 is approximately 20 times more prevalent (0.6%) [24] than the estimated allele frequency of *BRCA2* in the general worldwide Caucasian population [25]. This mutation with the same haplotype was also found in Finland [26,27]. In Iceland, it was the cause of female breast cancer in the majority (76%) of 21 high-risk breast cancer families studied [28]. In nine of those 16 families, male breast cancer was also present [28]. In 632 Icelandic breast cancer cases unselected for a family history, 7.7% of female breast cancer diagnosed at any age and 24% of those diagnosed at age 40 years or younger carried the *BRCA2* 999del5 mutation [24]. This mutation is also responsible for a proportion of prostate cancer, as it accounted for 3.1% (in two out of 65 individuals) of prostate cancer cases in a population-based series of cases [29]. Because this is the only *BRCA2* mutation found in Iceland, genetic testing can be targeted to this mutation. Second, because there are a large number of individuals, both symptomatic and asymptomatic, who carry this mutation, it may be possible to develop more accurate risk estimates for mutation carriers. Age-specific penetrance has been calculated to be 17% by age 50 years and 37.2% by age 70 years [30]. This is a lower frequency than that reported in other studies of *BRCA1* and *BRCA2* penetrance.

Three founder mutations have been observed in Ashkenazi Jewish breast and ovarian cancer patients. The *BRCA2* 6174delT mutation has been seen only in Ashkenazi Jews [31], with a frequency of 0.9–1.5% [32,33]. The founder *BRCA1* 185delAG mutation, with a frequency of 0.8–1.1% in Ashkenazi Jews [32,34], is also observed in Sephardic Jews, indicating an older origin. The 185delAG mutation has also been observed in individuals of English origin but on a different haplotype, which suggests a different origin. The third founder mutation, *BRCA1* 5382insC, has a frequency of 0.13–0.3% in Ashkenazi Jews. The 5382insC mutation is observed in many populations, and the vast majority of carriers share the same core haplotype (Szabo C, personal communication). The population prevalences for these three mutations combined is 2–2.5% [32–34], which is approximately 10–50 times higher than the allele frequency in the general population. Few other *BRCA1* or *BRCA2* mutations have been identified in Jewish breast or ovarian cancer cases. In this population, approximately 30% of breast cancers diagnosed at less than 40 years of age and 39% of ovarian cancers diagnosed at less than 50 years of age are caused by these mutations [35,36]. Thus, Ashkenazi Jewish women with breast or ovarian cancers have a much higher probability than non-Jewish women of being *BRCA1* or *BRCA2* mutation carriers. Because these mutations are so common in Ashkenazi Jewish women, they are commonly tested as a panel, regardless of whether a mutation has already been identified in a family member. A woman may carry a second mutation not present in the first family member tested and, by testing the panel, it is detected. Without knowledge of the founder mutations, a false-negative test result for an individual with a mutation-specific test could result.

Even among families with founder mutations, there appear to be differences in age of onset of cancer and in the type of cancers that develop [28,37–39]. This suggests that there are both genetic and lifestyle factors that modify penetrance of *BRCA1* and *BRCA2*. By studying a cohort of individuals with the same mutation, one may be able to distinguish factors that affecting penetrance, because there will not be a confounding effect from genotype–phenotype correlations from location of the *BRCA1*/*BRCA2* mutation in the individual. Once a risk factor is identified in one subgroup of mutation carriers it would need to be tested across other mutation carriers. Subsequently, it

would need to be tested in a population-based case–control study, in order to determine how important the risk factor is in the general population.

Other genes

BRCA1 and *BRCA2* mutations are certainly important determinants of risk for breast and/or ovarian cancers, but they are not the only ones. Many women, who have a family history of breast and/or ovarian cancer and do not have a *BRCA1* or *BRCA2* mutation, may have a mutation in undiscovered genes. After accounting for *BRCA1* and *BRCA2,* Peto *et al* [12] suggested that there are several other genes, possibly of lower risk, that account for a proportion of breast cancers. This complexity makes localizing additional genes problematic. Studying families identified from populations in which there are likely to be founder mutations may be extremely useful for localizing additional genes. For example, in Iceland researchers may have been able to localize *BRCA2* by studying male breast cancer cases from high-risk families and looking for regions of the genome with excess sharing. Researchers have suggested studying high-risk Ashkenazi Jewish breast cancer families that do not have a *BRCA1* or *BRCA2* mutation in order to localize *BRCA3*. Localization will be promoted by minimizing the effects of genetic heterogeneity.

Conclusion

Founder mutations allow for focused scientific studies of penetrance, expression, and genetic and environmental modifiers of risk. The results from these studies may be very useful for understanding the role that these genes play in the incidence of breast cancer in order to target genetic testing, to provide individual risk assessment, and to design better therapeutic strategies. Localization studies to find *BRCA3*, using founder populations, may be more successful than traditional linkage studies, which have not yet yielded positive localization results. These types of studies, utilizing founder populations and mutations, are not unique to breast cancer genetics, and are being used successfully to understand other diseases.

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