

## Short Communication

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# Genetic Testing for Breast Cancer Predisposition in 1999: which Molecular Strategy and which Family Criteria?

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The usefulness of genetic testing for risk assessment relies on three parameters: the probability that a given phenotype reflects a genetic trait, the genetic heterogeneity, and the allelic heterogeneity. Concerning breast cancer genetic testing, all these parameters preclude easy genetic diagnosis of a woman with a breast cancer family history and require careful interpretation particularly in the case of a negative result. However, once a mutation has been identified in a family, genetic testing can be offered to the relatives, with a clear positive or negative result.

Indeed, as breast cancer is a very common disease, family history may be due to chance without a predisposing gene segregating in the family. However, the probability of a family member being carrier of a predisposing gene can be evaluated taking into account his/her personal and family history (age and affection status for breast and ovarian cancer for all family members) under an established genetic model for breast cancer such as proposed by E. Claus [2,3]. Linkage analyses performed in a large set of families with at least four breast cancer cases, which indicate that BRCA1 and BRCA2 alterations account for the vast majority of familial forms of breast-ovarian cancers (95%) and for 65% of hereditary breast cancer-only

cases, provide evidence for the genetic heterogeneity of inherited breast cancers and the probable existence of still unidentified genes [5]. In addition, the BRCA1 and BRCA2 genes exhibit high allelic heterogeneity: 1.070 different germline variants of which 664 are inactivating mutations have been reported in the international database for BRCA1 and BRCA2 mutations (the Breast Cancer Information Core (BIC)). Only in a few populations (e.g. Icelandic, Ashkenazi Jewish) is breast cancer predisposition primarily due to a small number of founder mutations. Truncating mutations involving point or small size alteration have been predominantly reported, however, large rearrangements may occur in 10% to 25% of BRCA1 truncating mutations [6,7]. In addition, about 10% of the reported mutations are missense mutations. Except for a few cases, their functional relevance remains to be clarified.

The strategy of molecular analysis in women with a breast cancer family history must take into account all these difficulties and relies on: the number of available cases in the family, the choice of the index case, the existence of a founder effect, the nature of the family history. Since the indirect approach by linkage analysis will be applicable in very few families [4] direct analysis for mutation will be performed, generally with a screening method for point or small size mutations initially to save costs. The probability of detecting a point mutation was estimated to be about 63% in large families with disease due to BRCA1 [5]. It must be emphasized that this low detection rate is due to both the incomplete sensitivity of the screening

methods and the existence of large rearrangements. Detection of large rearrangements, using Southern Blot analysis, should therefore be included in the mutation screening.

Ideally, to define the best mutation detection strategy for a given set of predisposed cases, we need to know the absolute number of expected mutations and their nature (truncating point mutations, large rearrangements, causal missense mutations). Lacking this information, it is useful in clinical practice to estimate the probability of finding a mutation according to the family history and the molecular analyses performed. If a laboratory accepts a detection rate as low as 20% i.e. studying 100 samples with a screening method for point mutations to identify 20 mutations, then a tested affected individual with a family history of breast cancer only will be required to have a predisposition probability above 45%. A mean probability of 45% corresponds to two sisters affected with breast

cancer at 45 and 55 years [3]. Finally, it must be kept in mind that when screening a large number of samples becomes less work and cost intensive, a lower detection rate will be acceptable and therefore genetic testing criteria will be relaxed.

## References

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