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Review

Gene analysis techniques and susceptibility gene discovery in non-BRCA1/BRCA2 familial breast cancer

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ABSTRACT

Breast cancer is the leading cause of cancer deaths in females worldwide occurring in both hereditary and sporadic forms. Women with inherited pathogenic mutations in the *BRCA1* or *BRCA2* genes have up to an 85% risk of developing breast cancer in their lifetimes. These patients are candidates for risk-reduction measures such as intensive radiological screening, prophylactic surgery or chemoprevention. However, only about 20% of familial breast cancer cases are attributed to mutations in *BRCA1* and *BRCA2*, while a further 5–10% are attributed to mutations in other rare susceptibility genes such as *TP53*, *STK11*, *PTEN*, *ATM* and *CHEK2*. A multitude of genome wide association studies (GWAS) have been conducted confirming low-risk common variants associated with breast cancer in excess of 90 loci, which may contribute to a further 23% of the heritability.

We currently find ourselves in "the next generation", with technologies offering deep sequencing at a fraction of the cost. Starting off primarily in a research setting, multi-gene panel testing is now utilized in the clinic to sequence multiple predisposing genes simultaneously (otherwise known as multi-gene panel testing). In this review, we focus on the hereditary breast cancer discoveries, techniques and the challenges we face in this complex disease, especially in the light of the vast amount of data we now have at hand. It has been 20 years since the first breast cancer susceptibility gene has been discovered and there has been substantial progress in unraveling the genetic component of the disease. However, hereditary breast cancer remains a challenging topic subject to common debate.

Contents

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Introduction

Breast cancer remains a common cancer-related mortality in females aged 20–59 worldwide and is estimated that more than 1 million women every year have this diagnosis [1]. Alone, it is expected to account for 29% of all new cancer cases amongst women [2]. Age standardized breast cancer incidence varies internationally although this variation may be accounted for by the increasing prominence of screening programs in the western world and under-reporting in developing countries [3]. Historically, the most prominent risk factors for the development of breast cancer were thought to be hormonally-related and more specifically related to both endogenous and exogenous exposure to estrogen [4,5].

However, the last 20 years have seen much focus on the genetic component of the disease and the associated increased risk of breast cancer development that occurs as a direct result (See Fig. 1). One large-scale epidemiological study demonstrated that the excess lifetime incidence of developing breast cancer is 5.5% for women with one affected first-degree relative and 13.3% for women with two affected first-degree relatives [6]. A further review by Evans et al. showed that familial relative-risk was approximately two-to four-fold greater for first-degree relatives of breast cancer patients compared with controls from the general population [7]. It was identified at an early stage that the familial component of the disease is more common in younger rather than older age groups [8]. Recent genome-wide association studies testing low-penetrance breast cancer susceptibility polymorphisms have demonstrated that breast cancer risk does not vary significantly with known environmental risk factors [9].

The first major breakthrough in hereditary breast cancer was the discovery through linkage analysis that deleterious mutations located on chromosome 17q21 predisposed to high-risk breast and ovarian cancer [10]. It was not until 1994 that *BRCA1* was isolated by positional cloning [11]. Within that year, a genomic linkage analysis was performed on high-risk families that were not linked to *BRCA1*, leading to the discovery of the second highly penetrant breast cancer predisposing gene, *BRCA2*, localized to chromosome 13q12-13 [12]. *BRCA1* and *BRCA2* act as tumor suppressor genes by recognizing DNA damage and participating in the repair process. *BRCA1*'s major role includes homologous recombination, nucleotide excision repair, checkpoint control and regulation of transcription. *BRCA2* is also involved in homologous recombination and mainly repairs double stranded breaks [13]. The likelihood of developing breast cancer amongst mutation carriers until the age of 80 years has been estimated to be 79.5% for *BRCA1* and 88% for *BRCA2* [14]. In a study conducted on 46,276 women with early-onset or familial breast cancer of different ethnicities, the frequency of truncating mutations in *BRCA1* and *BRCA2* were 7.2% and 5.3%, respectively [15]. Altogether, these genes only account for 12.5–31% of breast cancer in patients with high familial risk based on studies involving multiple ethnicities [16,17]. Screening for germ-line mutations in these genes is now becoming an integral part of genetic counseling and clinical practice to identify women at high-risk of developing breast cancer.

Recently there has been increased interest in other (non BRCA1/BRCA2) breast cancer susceptibility genes and their associated penetrance. A paper published by Stratton et al., in 2008 found that 80% of females with a history of breast cancer and/or significant family history who undergo genetic testing for BRCA1/2 mutations have a negative result [17]. Although most breast cancer cases are sporadic it is clear that other genetic mutations play a role in the development of familial cancer [18,19]. Such genetic mutations have become more understood due to new and more sophisticated genetic analysis techniques such as next generation sequencing panels [20]. In 2010 a study by Walsh et al. was successful in identifying pathogenic mutations in 21 genes associated with increased risk of development of both breast and ovarian cancer using next generation sequencing [20]. Although these genetic analysis techniques continue to improve there remains a paucity of knowledge with regard to non-BRCA1/BRCA2 genetic mutations and their associated cancer risks. However, it is likely that such genes and therapies targeting their associated mutations will come to play a pivotal role in treating familial breast cancer in the future. Therefore a review of the multiple techniques being used as well increasingly prominent non-BRCA1/2 genes seemed timely. This review aims to assess the current strategies being used to identify breast cancer susceptibility genes and examine the clinical implications of such mutations.

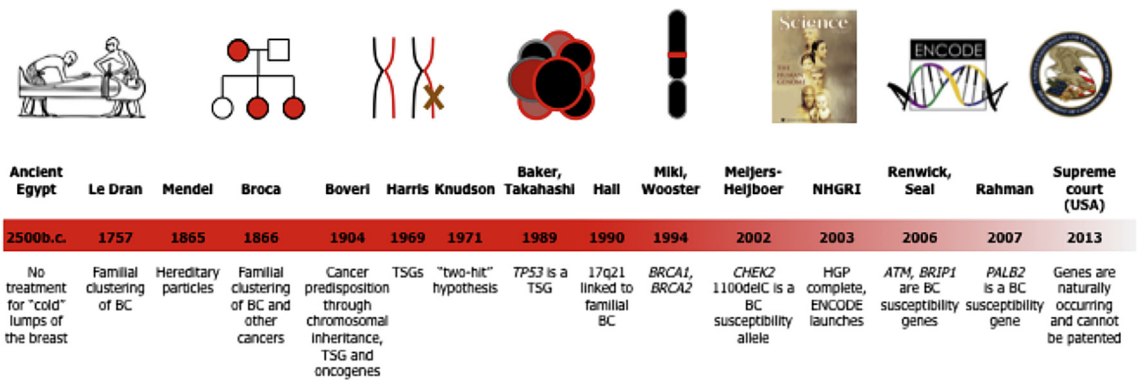

Figure 1. Landmarks in the understanding of hereditary breast cancer. BC: breast cancer, TSG: tumor suppressor gene; NHGRI: National Human Genome Research Institute; ENCODE: Encyclopedia of DNA elements; HGP: human genome project.