

Chapter 2

The Influence of Common Polymorphisms on Breast Cancer

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Abstract Breast cancer is one of the most frequently diagnosed cancers in the Western world and a significant cause of mortality worldwide. A small proportion of cases are accounted for by high-penetrance monogenic predisposition genes; however, this explains only a small fraction (less than 5%) of all breast cancers. Increasingly with advances in molecular technology and the development of large research consortia, the locations and identities of many low-penetrance genetic variants are being discovered. However, each variant has a very small effect similar to or smaller than many of the known environmental risk factors. It is therefore unlikely that these variants will be appropriate for predictive genetic testing, although they may identify novel pathways and genes which provide new insights and targets for therapeutic intervention. The future challenges will be identifying causal variants and determining how these low-penetrance alleles interact with each other and with environmental factors in order to usefully implement them in the practice of clinical medicine. Furthermore, it is clear that breast cancer comes in many forms with the tumour pathology and immunohistochemical profile already being used routinely as prognostic indicators and to inform treatment decisions. However, these indicators of prognosis are imperfect; two apparently identical tumours may have very different outcomes in different individuals. Inherited genetic variants may well be one of the other factors that need to be taken into account in assessing prognosis and planning treatment.

1 Introduction

Like most common cancers there is good evidence from population, family, and twin studies that shared genetic variants are contributing a proportion of risk [1, 2].

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Close relatives of an individual with breast cancer have an increased risk of developing the disease. In some (relatively rare) families there is a striking, dominant pattern of breast cancer, often in association with ovarian cancer. In these families, a likely explanation is a dominantly inherited rare genetic variant (mutation) with a high life-time penetrance for breast (and ovarian) cancer. The two most frequently mutated high-penetrance breast cancer genes are *BRCA1* and *BRCA2* [3]. The chance of breast cancer in a family being due to a single dominantly inherited gene increases with an increasing number of affected relatives; young age at onset and multiple primary tumours in an individual are characteristic of genetic predisposition, and these features are often used to select individuals for genetic counselling and genetic testing to determine if there is a high-risk gene mutation present in the family [4]. The lifetime age-related penetrance in a family that was ascertained because of multiple affected family members can be as high as 80% by 70 years of age [5]. However, it is clear that the penetrance of these high-risk genes varies between individuals and between families. At least some of this variation is associated with the presence of common genetic polymorphisms [6]. In many families with clustering of breast cancer, the pattern is less striking than in families with a *BRCA1* or *BRCA2* mutation. Figure 2.1 illustrates a pattern of inheritance in a family that is likely to have arisen because of a *BRCA1* gene mutation. Figure 2.2 is a family unlikely to have arisen as a result of a *BRCA1* or *BRCA2* mutation but also unlikely to have occurred entirely by coincidence; this familial cluster of breast cancers is most likely to have arisen because of a combination of shared low-penetrance genes and environmental factors.

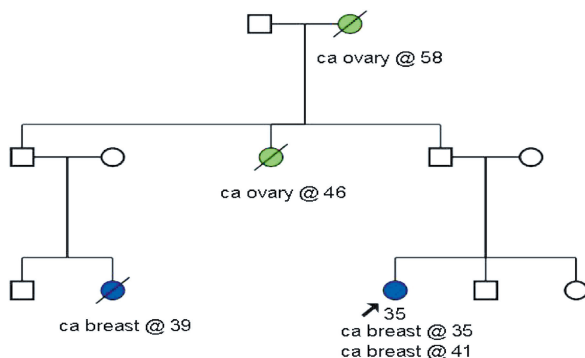
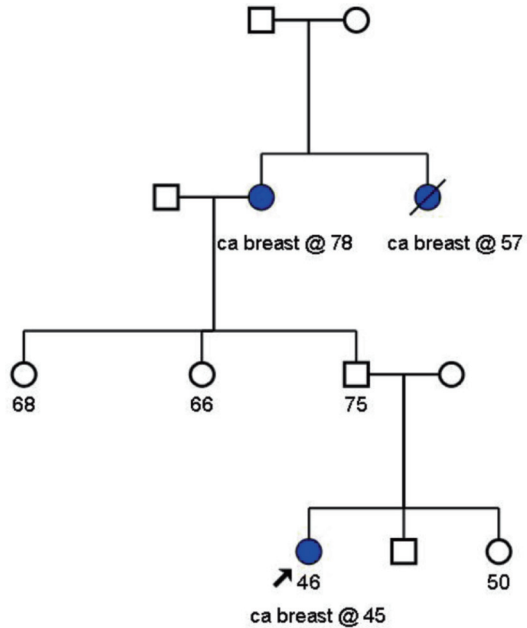


Fig. 2.1 Family history likely to be due to a *BRCA1* gene mutation

2 Breast Cancer Epidemiology

Breast cancer is one of the commonest cancers in the Western world and the incidence has been increasing over the last 25 years particularly in the more frequently affected post-menopausal age groups (<http://info.cancerresearchuk.org/cancerstats/types/breast/>). The strongest risk factors for breast cancer are sex (male breast cancer

Fig. 2.2 Family history is likely due to low-penetrance breast cancer risk alleles
BRCA1 gene mutation



incidence is much lower than for females) and age (in the UK and USA 80% of all breast cancers are diagnosed in women over 50 years of age). Obesity, early age at menarche, late age at menopause, late age at first birth, use of hormone replacement therapy after menopause, current use of oral contraceptive pills, sedentary lifestyle, and alcohol consumption are all factors that have been reported to impact on breast cancer risk. Some of these factors are entirely environmental (e.g. oral contraceptive pill use) and some such as obesity are a combination of complex genetic traits, lifestyle, and environment. Changes in lifestyle can exert an effect on breast cancer risk over a relatively short time scale [7, 8].

3 Breast Cancer Biology

Breast cancer is clearly both pathologically and molecularly more than one disease [9]. Routine pathological examination can and is used to subdivide tumour types since these give information about the likely prognosis and the need for additional treatment (surgery, hormonal manipulation, cytotoxic, or targeted drugs) [10, 11]. In addition to studying the morphological features of a breast tumour, the tissue will be examined using immunohistochemistry to determine, for example, whether a tumour has oestrogen receptors (ER positive) or not (ER negative). Most breast cancers (80%) express oestrogen receptors (are ER positive) and are therefore likely to respond to anti-oestrogen treatments. More recently amplification of

a transmembrane tyrosine kinase epidermal growth factor receptor HER2 has been clearly associated with a poor prognosis. Only a small proportion of breast cancers (<20%) show overexpression of HER2 but the recent development of therapeutic antibodies targeted at HER2 has rapidly established a need to identify those patients who might benefit from this targeted therapy [9, 12].

Increasingly sophisticated molecular techniques are now being used to analyse RNA and DNA extracted from tumours and identify several different molecular subgroups of breast cancer that are associated with differing clinical outcomes [13–15]. Despite this increasing sophistication of analysis of tumour types and the broad association of patterns of pathological or molecular features with overall prognosis, it is still not possible to precisely predict for any single individual when or where they will relapse from a tumour with any measure of certainty.

Black African women are known to develop breast cancer at a younger average age than white Caucasian populations and for breast tumours to be more likely to have adverse prognostic characteristics, specifically more oestrogen receptor negative tumours [16, 17]. This could be due to different genetic backgrounds and the presence of more low-penetrance risk alleles predisposing to ER-negative rather than ER-positive breast cancers in association with Black African ancestry. Breast cancer in younger women relative to post-menopausal women typically involves a higher prevalence of tumour types with adverse pathological features [18, 19]. This may be due to a difference in either the host environment, causative factors (genetic and environmental), or both. Female *BRCA1* gene mutation carriers are much more likely than most women to be affected with breast cancer at young ages but even in comparison to young women without *BRCA1* mutations, the likelihood of an ER-negative breast cancer developing in a *BRCA1* gene mutation carrier is extremely high [20]. This suggests that the high-risk gene mutation may be facilitating a particular molecular pathway of tumour evolution.

4 Breast Cancer Diagnosis

The diagnosis of breast cancer may be based on clinical examination and radiological features but a definitive diagnosis requires a pathological assessment of tumour tissue. This gives information about the growth rate of tumour cells (tumour nuclear grade is made up of a combined score where the pathologist assesses tubule formation, nuclear pleomorphism, and mitotic count), the type of breast cancer (e.g. ductal or lobular or one of the special subtypes), and with specific antibody stains the immunohistochemical profile (usually at least ER and HER2 receptor status). Clinical examination and radiological features plus tumour excision and removal of some or all of the axillary lymph nodes give information about tumour stage. The TNM system of staging is commonly used – T [tumour size], N [involvement of lymph nodes], and M [distant metastases]. Imaging of other areas of the body (lungs, liver, bone) is often included at baseline. In reality it is relatively uncommon for breast cancer to present with spread beyond axillary lymph nodes [21]. Once breast cancer has spread beyond the locoregional lymph nodes, it is extremely unlikely to

be cured. Both clinical and pathological features of a breast cancer have implications for prognosis and treatment.

5 Breast Cancer Treatment

Surgery: approaches to breast cancer management initially centred around mastectomy; however, it is now clear that since early-stage breast cancer patients are equally well treated with local wide excision and breast radiotherapy, the extent of surgery for a small breast cancer may be a matter of personal choice [22, 23]. Surgical excision of axillary lymph nodes is important for prognosis and to aid decisions about adjuvant therapy but more recently again the approach has moved towards sampling of nodes likely to be involved rather than removing all possible lymph nodes from the axilla [24].

Hormonal manipulation: since the earliest reports of the ability of even advanced breast cancer to respond to the removal of circulating oestrogen in 1896, oophorectomy and ovarian ablation to prevent oestrogen production in premenopausal women and pharmacological approaches to block oestrogen receptors or inhibit oestrogen production have been important strategies in breast cancer treatment [25]. It is now clear that in general only oestrogen receptor positive breast cancers are likely to respond to these approaches.

Cytotoxic therapies: Radiotherapy to the breast after breast conserving surgery and to the chest wall after mastectomy reduces the risk of local recurrence of breast cancer. The radiation field may be extended to include the axilla in some cases. Radiotherapy is also frequently used to reduce pain from bone metastases and symptoms from brain metastases when breast cancer spreads to distant sites.

Breast cancers are often sensitive to a wide range of cytotoxic chemotherapy drugs of the anthracycline type (anti-tumour antibiotics that interfere with enzymes involved in DNA replication) and increasingly now taxanes (mitotic spindle poisons) are included in many first-line adjuvant chemotherapy regimens. For high-grade and particularly ER-negative breast cancers, adjuvant cytotoxic chemotherapy is clearly beneficial in reducing the risk of distant spread of the disease [26].

Novel targeted therapies: As the pathological and molecular complexities of breast cancer are unravelled, opportunities arise for the development of novel therapies that are specifically aimed at blocking or suppressing tumour promoting pathways or mechanisms. One example of a very successful new biological targeted therapy is Herceptin which is an antibody to the HER2 receptor and is highly effective at reducing the risk of recurrence and at treating metastatic breast cancer for breast tumours in which the *HER2* gene is amplified [27].

6 Breast Cancer Genetics

Breast cancer is one of the commonest cancers in women in the western world. It is likely that all women who develop breast cancer have some genetic susceptibility.

Although only about 12% have one affected close relative, risk for breast cancer increases with increasing numbers of affected relatives [28]. This reflects the increasing likelihood of a high-penetrance dominant susceptibility gene segregating in a family with multiple affected close relatives. The majority of familial cases, however, are likely to be due to a combination of numerous common genetic variants that slightly increase the individual risk of breast cancer when compared to the population average (<1.5 fold increase per allele) [29]. These low-penetrance risk allele effects are likely to be multiplicative [30]. Rare mutations in other genes have also been implicated in relatively low-penetrance (two- to threefold increase) breast cancer susceptibility [31]. Only a rather small percentage of all cases (almost certainly less than 5%) are likely to be carriers of a high-risk susceptibility gene such as *BRCA1*, *BRCA2*, or *TP53* [3].

The average age of diagnosis of breast cancer in a white Caucasian population is around 60–65 years. Less than 20% of breast cancers are diagnosed under 50 years of age and only 5–10% under 40 years. The proportion of young onset breast cancers that are due to a highly penetrant single dominantly inherited breast cancer predisposition gene is higher than in later onset breast cancer cases [32, 33]. There is evidence of variation in the prevalence of pathological subtypes and the average age of onset of breast cancer in different age groups, in different geographical areas, and in different ethnic groups [16, 34]. These observations imply that genetic factors are important in breast cancer aetiology but that it is important to recognise that breast cancer is not a single disease entity, risk factors (including genetic risk factors) may vary for each different breast cancer subtype.

7 Gene Discovery

There are a variety of approaches that have been taken to identifying breast cancer predisposition genes, the chosen approach depends on the underlying genetic model and different methods allow the discovery of different types of genetic predisposition.

7.1 Linkage Analysis

Early breast cancer segregation analyses found that an autosomal dominant, rare, highly penetrant gene (or genes) was the most likely model that fit the available population data [1, 35]. Initial attempts to find breast cancer predisposition genes focused on familial multiple cases with early onset. The *TP53* gene was the first identified through the very striking clinical phenotype described by Li and Fraumeni [36–38], the *BRCA1* gene was mapped in the same year to chromosome 17 and *BRCA2* followed a few years later [39–42]. No further such high-penetrance genes have been identified to date [43]. There may be unique families with a dominantly transmitted mutation but traditional linkage studies using groups of families would not be able to detect such a gene. However, the majority of familial breast cancer

clusters are now thought to be due to co-inheritance of multiple lower penetrance genetic variants. Genome-wide linkage analysis may be successful in detecting further loci of interest in familial cases [44].

7.2 *Candidate Gene Resequencing*

Examination of genotypes in familial cancer cases compared to population controls has become easier with the development of faster and more cost-effective molecular techniques. Taking a candidate gene approach, rare pathogenic mutations in several genes have been found at significantly higher frequencies in familial cases compared with controls. These are estimated to confer a modest increase in relative risk of developing breast cancer of the order of two to three times the population risk. The DNA repair genes have been particularly rewarding candidates for this type of investigation [45–47].

7.3 *Genetic Association Studies*

Following the success of linkage studies to identify rare mutations with a high penetrance in genes such as *TP53* and *BRCA1/2*, association studies have been used to identify common mutations with low risk. This statistical approach compares the frequency of single nucleotide polymorphisms (SNPs) in unrelated disease cases and healthy controls. SNPs with frequencies which differ significantly between cases and controls mark the vicinity of disease causing alterations, even if they themselves are not responsible. Genome-wide association (GWA) studies scan the entire genome for SNPs affecting a certain disease without a prior hypothesis of likely candidate genes or knowledge of disease pathogenesis. As a result of this unbiased approach, many novel pathways and genes have been identified that would not be candidates otherwise and may provide vital new insights and targets for therapeutic intervention.

To date, nine genes with relative risks of 1.1–1.9 have been identified by GWAs [30–54] which account for approximately 4% of familial risk when their effects are combined (Table 2.1). Further GWAs are currently underway and a second phase of the Wellcome Trust Case Control Consortium will provide genotypic data from 6,000 controls. However, even accounting for all known loci, including high-risk genes such as *BRCA1*, *BRCA2*, and *TP53* with relative risks of 5–10, at least 70% of the familial risk for breast cancer remains unexplained. Although the risk associated with some of the low penetrance loci may increase when causal rather than associated variants are determined, further loci undoubtedly remain to be detected. As genetic linkage studies have failed to identify further major breast cancer genes [43], much of the remaining genetic susceptibility is likely to be due to low-penetrance genes and perhaps rare genetic variants which are more suited to discovery by GWAs and sequencing than by linkage studies [55].

Table 2.1 Loci associated with breast cancer

Study	Cases	Controls	SNPs	Phenotype	Population	Associations	Odds ratio	P value
Easton et al. [30]	408	400	266, 722	Invasive, onset <60, positive family history, BRCA1/2 -ve	UK	FGFR2	1.26	4×10^{-16}
						TNRC9	1.11	10^{-7}
						MAP3K1	1.13	4×10^{-6}
						LSP1	1.07	8×10^{-6}
Hunter et al. [48]	1, 183	1, 185	528, 173	Invasive, post-menopausal, sporadic	USA, self-reported Caucasian	H19	0.96	7×10^{-6}
						8q24.21	1.08	2×10^{-7}
						FGFR2	1.23	1.2×10^{-5}
WTCCC [65]	1, 004	1, 464	15, 436	Invasive, positive family history, BRCA1/2 -ve	UK, self-reported Caucasian	MUC1 ^a	1.25	1.3×10^{-4}
Stacey et al. [66]	1, 600	11, 563	311, 524	Invasive, median onset 56.3 years, 4.9% BRCA2	Iceland	TNRC9	1.23	4.7×10^{-6}
						2q35	1.19	9.2×10^{-6}
Kibriya et al. [67]	30	30	203, 477	Invasive, BRCA1/2 -ve	USA, Canada, Germany, Caucasian, Hispanic, African American	GLG1 ^{a,b}	-	4.04×10^{-7}
						UGT1 ^{a,b}	-	4.89×10^{-7}

Table 2.1 (continued)

Study	Cases	Controls	SNPs	Phenotype	Population	Associations	Odds ratio	P value
Gold et al. [50]	249	299	435, 632	Breast cancer, median onset 55, positive family history, BRCA1/2 -ve	USA, Canada, Israel, genetically isolated Ashkenazi Jews	FGFR2	1.26	1.5×10^{-5}
						6q22.33	1.41	2.9×10^{-8}
Zheng et al. [54]	1, 505	1, 522	607, 728	Breast cancer	Chinese	6q25.1	1.56	1.4×10^{-5}
Cox et al. [68]	16, 423 12, 946	17, 109 15, 109	9	Invasive, sporadic and positive family history	18 European and two Asian populations	ESR1	0.88	5.7×10^{-7}
						CASP8 TGFB1	1.08	1.5×10^{-4}

^aNot replicated
^bResults from haplotype test

7.3.1 Breast Cancer Heterogeneity

Breast cancer is a heterogeneous disease that can be subdivided on the basis of conventional histology and immunohistochemical markers [56, 57] and gene expression profiles [13, 15]. The gene expression subsets are largely determined by levels of hormone receptor-related genes such as *ER*, *PR*, and *HER2* and, therefore, overlap largely with the histological subsets. For example, most basal-like subtypes of breast cancer are triple-negative breast cancer (ER–ve, PR–ve, HER2–ve). Luminal subtypes are typically ER positive. These subtypes of breast cancer are increasingly recognised as separate diseases with different outcomes [58]. Increasingly different treatment approaches are being considered for specific subtypes of breast cancer [59]. Characteristic morphological features have been highlighted in *BRCA1*, *BRCA2*, and other familial breast cancer groups [60–62]. Unsurprisingly perhaps, breast cancers arising in high-risk gene carriers can also be demonstrated to broadly share molecular characteristics using a variety of genomic techniques [63, 64].

7.3.2 Common Genetic Variants and Breast Cancer Phenotype

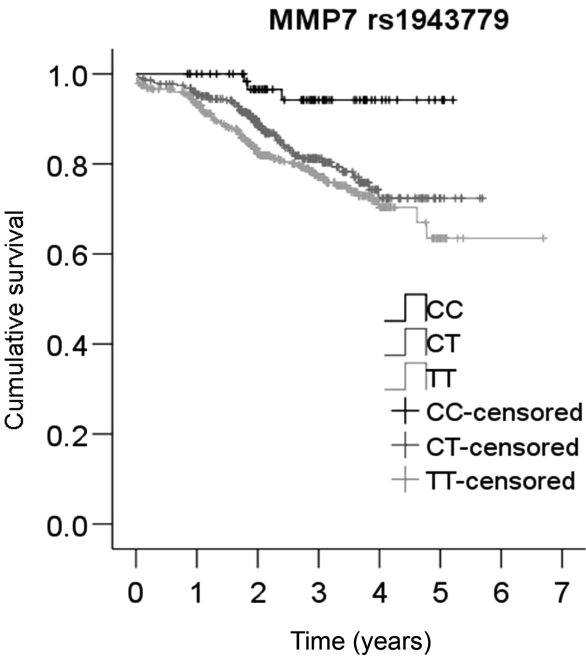
Recent studies have demonstrated that some of the associations between common genetic variants and the risk of developing breast cancer are probably specific to certain subgroups, broadly at the moment observed when ER-negative and ER-positive breast cancers are considered as separate groups [49, 66, 69]. This supports the concept that subtypes of breast cancer have different genetic components of risk. Many GWAs have failed to account for this heterogeneity which may have reduced their power and explain some of the failures to replicate previous findings [70]. Confining GWAs to subsets of breast cancer that show a strong component of genetic risk (by selecting cases with positive family histories) or a specific subgroup of breast tumour type will reduce genetic heterogeneity and increase power to detect subtype specific effects and novel genes.

7.3.3 Common Genetic Variants and Prognosis

Recent studies have suggested that the prognosis of breast cancer is also influenced by genetic factors. The process of tumour development and progression varies considerably between patients. The known tumour features that are used to predict prognosis are noted at the time of presentation – tumour size, grade, ER status, HER2 status, locoregional lymph node involvement, etc. A variety of prognostic algorithms are used clinically to predict risk of relapse, new molecular profiles are being tested [10, 71, 72]. None predict with certainty for an individual and it is realistic to expect that individual genetic background will affect response to tumour growth and metastasis as well as to risk. Recent data from a population-based study indicated that daughters and sisters of a proband with poor prognosis had a 60% higher 5-year breast cancer mortality compared to those of a proband with good prognosis (hazard ratio 1.6, P for trend 0.002), suggesting an inherited component to prognosis [73].

In a pilot study to explore the role of common genetic variants in breast cancer prognosis, 30 candidate genes were selected for investigation. Tagging SNPs across the 30 candidate genes were typed in 1,001 individuals from the Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) cohort, three genes were identified that influence distant disease-free survival (DDFS) times and these effects are independent of tumour-specific factors [74] (Fig. 2.3). To date, however, there have been no GWAs to identify genes that influence outcome after diagnosis of breast cancer.

Fig. 2.3 Kaplan Meir survival analysis showing that the genotype of SNP rs1943779 in the MMP7 gene is significantly associated with the chance of relapsing after a breast cancer diagnosis



7.3.4 Host Response to Treatment

Pharmacogenetics is the study of genetic variants that influence the response to drugs, for example by affecting the rate and efficiency of drug metabolism. Clearly then genetic variation may well influence prognosis since in many cases the prognosis of the individual is being influenced by the treatment administered. In diseases other than breast cancer, genetic factors have been demonstrated to affect the efficacy of treatments by altering their absorption and receptor-ligand interactions [75]. In breast cancer, a recent study has shown that genetic variants of CYP2D6 and CYP2C19 may influence prognosis by altering the metabolism and subsequent efficacy of tamoxifen in ER-positive breast cancer; however, the evidence is conflicting

[76, 77]. Mutations of NQO1 have also been shown to influence prognosis in breast cancer by impairing the response of patients to epirubicin but this observation has not yet been confirmed by others [78].

7.3.5 Breast Cancer Growth and Metastases in the Host Environment

Breast cancers arise due to the accumulation of multiple genetic and epigenetic perturbations that enhance the growth and division capability of the cell of origin. More rapid proliferation in the absence of any of the important regulatory mechanisms increases the likelihood of cellular DNA acquiring new somatic and epigenetic mutations during replication. Loss of normal mechanisms for DNA repair and for apoptosis (programmed cell death) leads to disordered growth and eventually the accumulation of more mutations enhancing the ability of the tumour to invade and metastasise which are the hallmarks of a malignant tumour. Several mechanisms may be important for preventing malignancy and many of these are under genetic control. The immune system, DNA repair genes, and host stromal elements (e.g. matrix metalloproteinases) are all good biological candidates for a potential role in individually variable responses to tumourigenesis and the development and growth of metastases. Breast cancers typically spread to bone, brain, lung, and liver, but the site of metastasis is unpredictable even when similar tumours are compared. Germline polymorphisms have been shown to contribute to these variations in the site of metastasis [79]. In human breast cancer, inherited polymorphisms in *Brd4* and *Sipa1* (with which *Brd4* interacts) have been shown to alter protein expression and are predictive of metastasis and increased expression of *TNRC9* is associated with metastasis to bone [80–82].

7.3.6 Challenges in Genome-Wide Association Studies

Despite the success of GWAs many limitations and challenges remain. Many of the susceptibility alleles identified are so common that a high proportion of the general population are carriers with small risk. It is, therefore, unlikely that these SNPs will be appropriate for predictive testing until the estimated risk associated with them is increased by identifying causal alleles or combinations of associated variants [83, 84]. Once a variant has been reproducibly associated with disease the next step is to perform functional studies that identify causal mutation(s), which may differ from the associated variant and which may lead to potential new avenues for therapeutic intervention. Functional analyses aim to demonstrate that causal mutations alter the expression or function of a gene resulting in biologically plausible consequences. For example, a comprehensive study of *CTLA4* variants in autoimmune disease demonstrated that the causal allele is located in the regulatory 3' untranslated region of the gene rather than the leader peptide which contained the associated variant [85].

In order for future GWAs to detect further susceptibility loci, it is anticipated that larger numbers of cases and controls will be required. This may be achieved as genotyping costs fall and as more large consortia come together to combine data across

multiple studies. Previous GWAs of breast cancer have relied on approximately 15,000–530,000 SNPs to capture information from an estimated 7–15 million SNPs in the genome through linkage disequilibrium (LD). In some regions, however, the coverage is incomplete resulting in a loss of power to detect associated variants in these areas. Following completion of phase II of the HapMap project, which characterised over 3.1 million SNPs [86], and the introduction of high-density chips that contain over 2 million SNPs and copy number variations, new GWAs will provide more comprehensive scans of the genome that will lead to the identification of novel susceptibility genes.

In general, association studies are required to note the ethnicity of cases and controls and minimise bias due to the selection/matching of particular individuals from a wider population since population stratification can lead to false positives. This is especially true for breast cancer which appears to be more severe in women with African ancestry [87]. Prior to the analysis of GWA data, it is therefore prudent to test the homogeneity of the sample and exclude any outliers. The PLINK program [88] uses a multidimensional scaling analysis of genome-wide average identities by state (IBS) and with additional data from Caucasian, African, and Asian populations from the HapMap project [86] was used, for example, to assess ethnic homogeneity in 1,001 British breast cancer cases prior to association testing [74]. Plotting the first two components from the multidimensional scaling analysis, which represent geographic and genetic variation, clearly identified three distinct clusters that correspond to African, Asian, and Western European ancestries (Fig. 2.4). This information was used to ensure that variation in SNP profiles resulting from

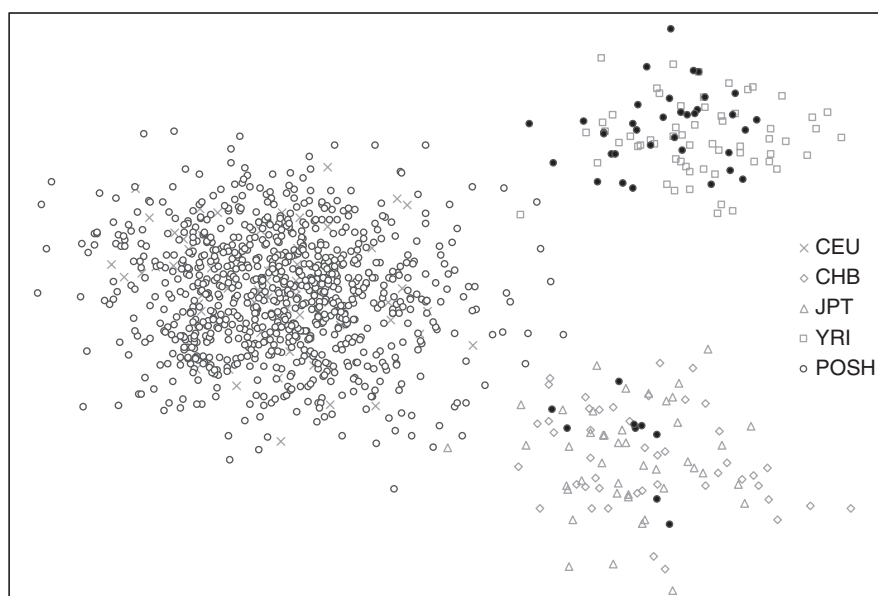


Fig. 2.4 Identifying evidence of population stratification

different ethnic backgrounds were not confounding the analysis of SNPs associated with disease characteristics [74].

GWAs were developed with the hypothesis that common diseases, such as breast cancer, are caused by common, low-penetrance variants. However, if rarer variants with higher penetrance are responsible, future GWAs will need to genotype more people and SNPs to detect this type of variant and genome-wide linkage analysis may be an alternative approach [44]. By sequencing the genomes of 1,000 people, the 1,000 genomes project aims to produce a genome-wide map of variations found in 1% of the population, 10 times rarer than those provided by the HapMap project. This project will also characterise structural variations of the genome such as rearrangements, deletions, or duplications of the genome which may play a role in susceptibility to diseases. This information will facilitate the detection of causal variants by identifying almost all variants in a region associated with disease and helping to select variants for functional studies.

8 Summary

The study of genetic influences in breast cancer is complex. Careful case selection is important with account being taken of ethnic homogeneity, disease phenotype, and environmental risk factor exposure. The translation of current knowledge about common polymorphisms and breast cancer susceptibility has potential for early detection and risk stratification in future. Targeted breast cancer management strategies may require not only tumour molecular profiling but also knowledge of an individual's genetic susceptibility to develop metastatic disease. There is still a great deal more that needs to be discovered and understood before this type of genetic knowledge will find a valid place in clinical care of individuals and families with breast cancer.

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