Chapter 2
The Influence of Common Polymorphisms on Breast Cancer

Diana Eccles and William Tapper

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].

D. Eccles (✉)

Human Genetics and Cancer Sciences Divisions, School of Medicine, University of Southampton, Southampton University Hospitals NHS Trust, SO16 6YD, UK
e-mail: d.m.eccles@soton.ac.uk

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 lifetime 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.
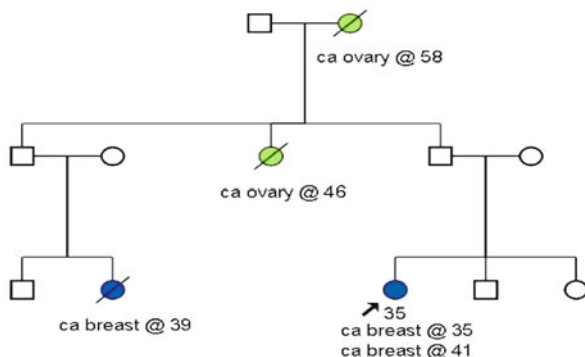

Fig. 2.1 Family history likely to be due to a *BRCA1* gene mutation

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
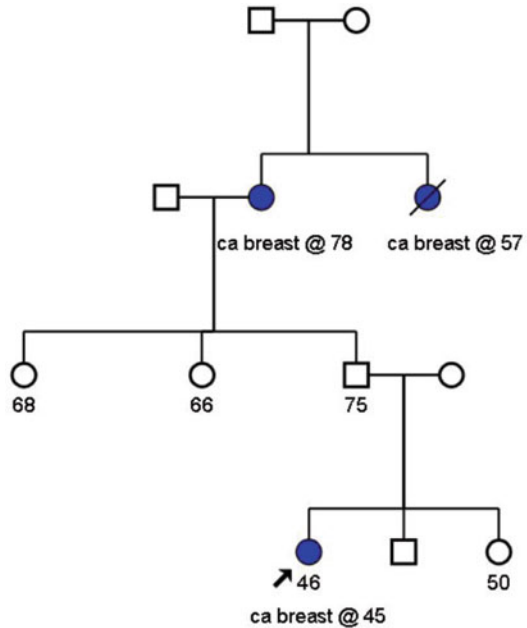
incidence is much lower than for females) and age (in the UK and USA 80% of all breast cancers are diagnosed in women over 50 years of age). Obesity, early age at menarche, late age at menopause, late age at first birth, use of hormone replacement therapy after menopause, current use of oral contraceptive 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}
						H19	0.96	7×10^{-6}
						8q24.21	1.08	2×10^{-7}
Hunter et al. [48]	1, 183	1, 185	528, 173	Invasive, post-menopausal, sporadic	USA, self-reported Caucasian	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 6q22.33	1.26 1.41	1.5×10^{-5} 2.9×10^{-8}
Zheng et al. [54]	1, 505	1, 522	607, 728	Breast cancer	Chinese	6q25.1 ESR1	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	CASP8 TGFB1	0.88 1.08	5.7×10^{-7} 1.5×10^{-4}

[a]Not replicated
[b]Results 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 accounted 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 sigificantly associated with the chance of relapsing after a breast cancer diagnosis
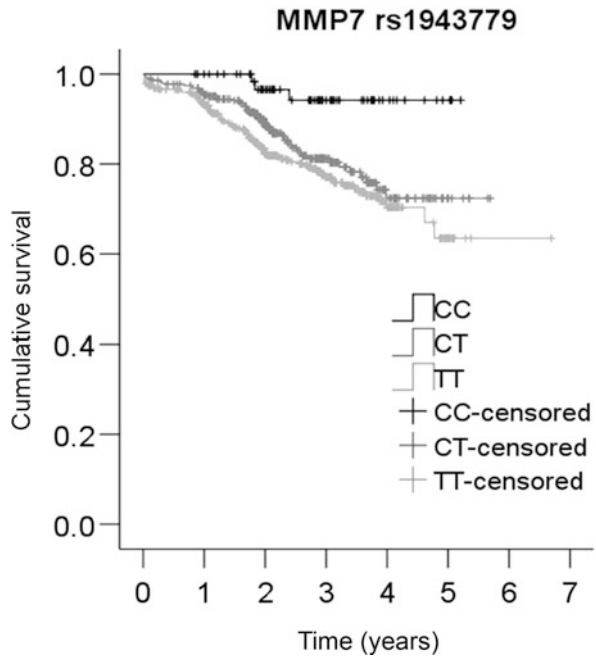
7.3.4 Host Response to Treatment

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
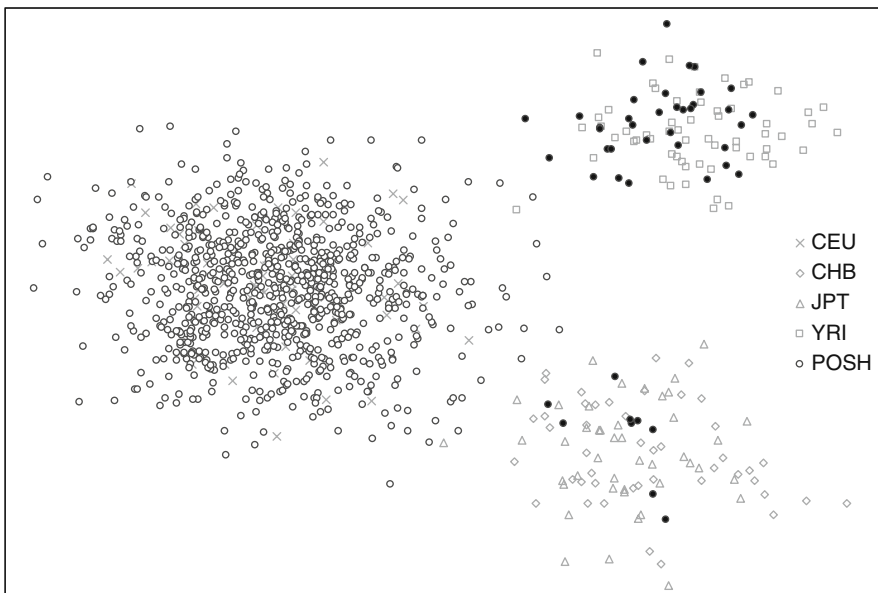

Fig. 2.4 Identifying evidence of population stratification

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.

References

1. Claus EB, Risch N, Thompson WD (1991) Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 48(2):232–242
2. Hartman M, Hall P, Edgren G et al (2008) Breast cancer onset in twins and women with bilateral disease. J Clin Oncol 26(25):4086–4091
3. Stratton MR, Rahman N (2008) The emerging landscape of breast cancer susceptibility. Nat Genet 40(1):17–22
4. Antoniou AC, Hardy R, Walker L et al (2008) Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet 45(7):425–431
5. Ford D, Easton DF, Stratton M et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 62(3):676–689
6. Antoniou AC, Spurdle AB, Sinilnikova OM et al (2008) Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. Am J Hum Genet 82(4):937–948

7. Wiseman RA (2004) Breast cancer: critical data analysis concludes that estrogens are not the cause, however lifestyle changes can alter risk rapidly. J Clin Epidemiol 57(8):766–772

8. Ziegler RG, Hoover RN, Pike MC et al (1993) Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 85(22):1819–1827

9. Pakkiri P, Lakhani SR, Smart CE (2009) Current and future approach to the pathologist's assessment for targeted therapy in breast cancer. Pathology 41(1):89–99

10. Galea MH, Blamey RW, Elston CE, Ellis IO (1992) The Nottingham prognostic index in primary breast cancer. Breast Cancer Res Treat 22:207–219

11. Schmidt M, Victor A, Bratzel D et al (2008) Long-term outcome prediction by clinicopathological risk classification algorithms in node-negative breast cancer – comparison between Adjuvant! St Gallen, and a novel risk algorithm used in the prospective randomized Node-Negative-Breast-Cancer-3 (NNBC-3) trial. Ann Oncol 20(2):258–264

12. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672

13. Sorlie T, Perou CM, Tibshirani R et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98:10869–10874

14. Wessels LF, van Welsem T, Hart AA, van't Veer LJ, Reinders MJ, Nederlof PM (2002) Molecular classification of breast carcinomas by comparative genomic hybridization: a specific somatic genetic profile for BRCA1 tumors. Cancer Res 62(23):7110–7117

15. Perou CM, Sorlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752

16. Anderson WF, Rosenberg PS, Menashe I, Mitani A, Pfeiffer RM (2008) Age-related crossover in breast cancer incidence rates between black and white ethnic groups. J Natl Cancer Inst 100(24):1804–1814

17. Bowen RL, Duffy SW, Ryan DA, Hart IR, Jones JL (2008) Early onset of breast cancer in a group of British black women. Br J Cancer 98(2):277–281

18. Anderson WF, Chu KC, Chang S, Sherman ME (2004) Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 13(7):1128–1135

19. Walker RA, Lees E, Webb MB, Dearing SJ (1996) Breast carcinomas occurring in young women (<35 years) are different. Br J Cancer 74(11):1796–1800

20. Lakhani SR, Reis-Filho JS, Fulford L et al (2005) Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 11(14):5175–5180

21. Sobin LH (2003) TNM, sixth edition: new developments in general concepts and rules. Semin Surg Oncol 21:19–22

22. Veronesi U, Salvadori B, Luini A et al (1995) Breast-conservation is a safe method in patients with small cancer of the breast – long-term results of 3 randomized trials on 1,973 patients. Eur J Cancer 31A(10):1574–1579

23. Throckmorton AD, Esserman LJ (2009) When informed, all women do not prefer breast conservation. J Clin Oncol 27(4):484–486

24. Gui GP, Joubert DJ, Reichert R et al (2005) Continued axillary sampling is unnecessary and provides no further information to sentinel node biopsy in staging breast cancer. Eur J Surg Oncol 31(7):707–714

25. Piccart-Gebhart MJ (2004) New stars in the sky of treatment for early breast cancer. N Engl J Med 350(11):1140–1142

26. Clarke M (2006) Meta-analyses of adjuvant therapies for women with early breast cancer: the Early Breast Cancer Trialists' Collaborative Group overview. Ann Oncol 17(Supplement 10):x59–x62

27. Untch M, Gelber RD, Jackisch C et al (2008) Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 19(6):1090–1096

28. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including

58,209 women with breast cancer and 101,986 women without the disease. Lancet 358(9291):1389–1399

29. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA (2002) Polygenic susceptibility to breast cancer and implications for prevention. Nat Genet 31(1):33–36

30. Easton DF, Pooley KA, Dunning AM et al (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447(7148):1087–1093

31. Walsh T, King MC (2007) Ten genes for inherited breast cancer. Cancer Cell 11(2):103–105

32. Lalloo F, Varley J, Moran A et al (2006) BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. Eur J Cancer 42(8):1143–1150

33. Bonadona V, Sinilnikova OM, Chopin S et al (2005) Contribution of BRCA1 and BRCA2 germ-line mutations to the incidence of breast cancer in young women: results from a prospective population-based study in France. Genes Chromosomes Cancer 43(4):404–413

34. Anderson WF, Chen BE, Brinton LA, Devesa SS (2007) Qualitative age interactions (or effect modification) suggest different cancer pathways for early-onset and late-onset breast cancers. Cancer Causes Control 18(10):1187–1198

35. Eccles D, Marlow A, Royle G, Collins A, Morton NE (1994) Genetic epidemiology of early onset breast cancer. J Med Genet 31(12):944–949

36. Li FP, Fraumeni JFJ (1969) Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 71(4):747–752

37. Li FP, Fraumeni JF Jr, Mulvihill JJ et al (1988) A cancer family syndrome in twenty-four kindreds. Cancer Res 48(18):5358–5362

38. Malkin D, Li FP, Strong LC et al (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250(4985):1233–1238

39. Hall JM, Lee MK, Newman B et al (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250(4988):1684–1689

40. Miki Y, Swensen J, Shattuck-Eidens D et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266(5182):66–71

41. Wooster R, Neuhausen SL, Mangion J et al (1994) Localization of a breast cancer suscepti-bility gene, BRCA2, to chromosome 13q12-13. Science 265(5181):2088–2090

42. Wooster R, Bignell G, Lancaster J et al (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378(6559):789–792

43. Smith P, McGuffog L, Easton DF et al (2006) A genome wide linkage search for breast cancer susceptibility genes. Genes Chromosomes Cancer 45(7):646–655

44. Rosa-Rosa JM, Pita G, Urioste M et al (2009) Genome-wide linkage scan reveals three putative breast-cancer-susceptibility loci. Am J Hum Genet 84(2):115–122

45. Renwick A, Thompson D, Seal S et al (2006) ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet 38(8):873–875

46. Rahman N, Seal S, Thompson D et al (2007) PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet 39(2):165–167

47. Seal S, Thompson D, Renwick A et al (2006) Truncating mutations in the Fanconi ane-mia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet 38(11):1239–1241

48. Hunter DJ, Kraft P, Jacobs KB et al (2007) A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 39(7):870–874

49. Stacey SN, Manolescu A, Sulem P et al (2008) Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 40(6):703–706

50. Gold B, Kirchhoff T, Stefanov S et al (2008) Genome-wide association study provides evi-dence for a breast cancer risk locus at 6q22-33. Proc Natl Acad Sci USA 105(11):4340–4345

51. Argos M, Kibriya MG, Jasmine F et al (2008) Genomewide scan for loss of heterozygosity and chromosomal amplification in breast carcinoma using single-nucleotide polymorphism arrays. Cancer Genet Cytogenet 182(2):69–74

52. Newport M, Sirugo G, Lyons E et al (2007) Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet 39(11):1329–1337

53. Kibriya MG, Jasmine F, Argos M et al (2009) A pilot genome-wide association study of early-onset breast cancer. Breast Cancer Res Treat 114(3):463–477
54. Zheng W, Long JR, Gao YT et al (2009) Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 41(3):324–328
55. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273(5281):1516–1517
56. Abd El-Rehim DM, Pinder SE, Paish CE et al (2004) Expression of luminal and basal cytokeratins in human breast carcinoma. J Pathol 203(2):661–671
57. Makretsov NA, Huntsman DG, Nielsen TO et al (2004) Hierarchical clustering analysis of tissue microarray immunostaining data identifies prognostically significant groups of breast carcinoma. Clin Cancer Res 10(18 Pt 1):6143–6151
58. Sorlie T, Tibshirani R, Parker J et al (2003) Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 100:8418–8423
59. Turner NC, Reis-Filho JS, Russell AM et al (2007) BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 26(14):2126–2132
60. Lakhani SR (1999) The pathology of familial breast cancer: morphological aspects. Breast Cancer Res 1(1):31–35
61. Lakhani SR, Van D V, Jacquemier J et al (2002) The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 20(9): 2310–2318
62. Palacios J, Honrado E, Osorio A et al (2005) Phenotypic characterization of BRCA1 and BRCA2 tumors based in a tissue microarray study with 37 immunohistochemical markers. Breast Cancer Res Treat 90(1):5–14
63. Hedenfalk IA, Ringner M, Trent JM, Borg A (2002) Gene expression in inherited breast cancer. Adv Cancer Res 84:1–34
64. Jonsson G, Naylor TL, Vallon-Christersson J et al (2005) Distinct genomic profiles in hereditary breast tumors identified by array-based comparative genomic hybridization. Cancer Res 65(17):7612–7621
65. The Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447:661–678
66. Stacey SN, Manolescu A, Sulem P et al (2007) Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 39(7): 865–869
67. Kibriya MG, Jasmine F, Argos M et al (2009) A pilot genome-wide association study of early-onset breast cancer. Breast Cancer Res Treat 114(3):463–477
68. Cox A, Dunning AM, Garcia-Closas M, Balasubramanian S et al (2007) A common coding variant in CASP8 is associated with breast cancer risk. Nat Genet 39(3):352–358
69. Garcia-Closas M, Hall P, Nevanlinna H et al (2008) Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 4(4):e1000054
70. Amos CI (2007) Successful design and conduct of genome-wide association studies. Hum Mol Genet 16(R2):R220–R225
71. Ozanne EM, Braithwaite D, Sepucha K, Moore D, Esserman L, Belkora J (2009) Sensitivity to input variability of the adjuvant! Online breast cancer prognostic model. J Clin Oncol 27(2):214–219
72. Bueno-de-Mesquita JM, van Harten WH, Retel VP et al (2007) Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER). Lancet Oncol 8(12):1079–1087
73. Hartman M, Lindstrom L, Dickman PW, Adami HO, Hall P, Czene K (2007) Is breast cancer prognosis inherited? Breast Cancer Res 9(3):R39
74. Tapper W, Hammond V, Gerty S et al (2008) The influence of genetic variation in thirty selected genes on the clinical characteristics of early onset breast cancer. Breast Cancer Res 10(6):R108

75. Liu ZL, He B, Fang F, Tang CY, Zou LP (2008) Genetic polymorphisms of MC2R gene associated with responsiveness to adrenocorticotropic hormone therapy in infantile spasms. Chinese Med J 121(17):1627–1632
76. Schroth W, Antoniadou L, Fritz P et al (2007) Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 25(33): 5187–5193
77. Okishiro M, Taguchi T, Kim SJ, Shimazu K, Tamaki Y, Noguchi S (2009) Genetic polymorphisms of CYP2D6*10 and CYP2C19*2,*3 are not associated with prognosis, endometrial thickness, or bone mineral density in Japanese breast cancer patients treated with adjuvant tamoxifen. Cancer 115(5):952–961
78. Fagerholm R, Hofstetter B, Tommiska J et al (2008) NAD(P)H:quinone oxidoreductase 1 NQO1*2 genotype (P187S) is a strong prognostic and predictive factor in breast cancer. Nat Genet 40(7):844–853
79. Hsieh SM, Lintell NA, Hunter KW (2006) Germline polymorphisms are potential metastasis risk and prognosis markers in breast cancer. Breast Dis 26:157–162
80. Crawford NPS, Alsarraj J, Lukes L et al (2008) Bromodomain 4 activation predicts breast cancer survival. Proc Natl Acad Sci USA 105(17):6380–6385
81. Park YG, Zhao XH, Lesueur F et al (2005) Sipa1 is a candidate for underlying the metastasis efficiency modifier locus Mtes1. Nat Genet 37(10):1055–1062
82. Smid M, Wang Y, Klijn JG et al (2006) Genes associated with breast cancer metastatic to bone. J Clin Oncol 24(15):2261–2267
83. Gail MH (2008) Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. J Natl Cancer Inst 100(14):1037–1041
84. Pharoah PD, Antoniou AC, Easton DF, Ponder BA (2008) Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med 358(26):2796–2803
85. Ueda H, Howson JM, Esposito L et al (2003) Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 423(6939):506–511
86. Gibbs RA, Belmont JW, Hardenbol P et al (2003) The international HapMap project. Nature 426(6968):789–796
87. Bowen RL, Stebbing J, Jones LJ (2006) A review of the ethnic differences in breast cancer. Pharmacogenomics 7(6):935–942
88. Purcell S, Neale B, Todd-Brown K et al (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81(3):559–575