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Surveying germline genomic landscape of breast cancer

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Abstract The recent large genotyping studies have identified a new repertoire of breast cancer susceptibility genes and loci which are characterized by common risk alleles and low relative risks. Because of these properties, these loci explain a much larger proportion of the etiology of the particular cancers, described by the population attributable fraction (PAF), than of their familial risks. PAF is particularly suitable for ‘genomic landscaping’ because it defines the proportion of breast cancer explained by the variant under study. The joint PAF for the previously described high-penetrance alleles is about 1%, for moderate-penetrance alleles it is 1.5% and for low-penetrance susceptibility alleles it is 58%. The evidence appears compelling in pointing to the remarkably high population impacts of the recently described heritable loci compared to the ‘classical’ high-penetrance genes.

Keywords Familial risk · Population attributable fraction · Genotype relative risk · Cancer genetics

Recent studies on somatic alterations in breast cancer have revealed large numbers of mutated genes, the commonest ones of which have been referred to as ‘mountains’ and the rarer ones as ‘hills’ in the genomic landscape [1]. Among

germline mutations predisposing to breast cancer several variants have also been described, whereby the germline landscape of breast cancer susceptibility is taking form [2]. Along with the previously characterized high-penetrance genes, such as BRCA1 and BRCA2, moderate-penetrance and low-penetrance susceptibility alleles have recently been detected [3–7]. The level of penetrance is defined by the relative risk that the alleles inflict in mutation carriers. However, when the genomic landscape is being surveyed and the perspective is being widened over the individuals into the population, measures beyond the individual risk will be useful. The familial risk is one of them, but it is useful only if the causative variants are known [8], which is not the case with the newly detected low-penetrant variants of unknown function. Thus, the commonly cited low familial risks of the new variants are probably only the minimal estimates. The new variants are likely to be markers of rarer functional variants which would confer a higher familial risk, the magnitude of which can only be estimated once the functional variants have been identified [8]. A more robust measure is the population attributable fraction (PAF), which has many useful properties particularly for genomic landscaping. There it defines the proportion (etiological proportion) of the disease occurrence explained by the variant under study. We review some properties of PAF and apply these to the genes/loci that can be grouped by their variable penetrance [2].

The PAF of each variant shows its relative etiologic impact. Importantly, the PAF is identical for the marker and its linked (linkage disequilibrium $D' = 1.0$) causative variant, thus making it a more robust tool for genomic landscaping than the familial risk [8]. PAFs have been used extensively for environmental risk factors of diseases in order to rank them and to assess the prospective gains in disease prevention. Their use in cancer genetics is

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relatively new [5, 6, 9, 10], probably because the mutant variants of the ‘classical’ high-penetrance cancer genes are so rare that their contribution to the population burden is low compared to the high individual risks [7]. Some recent studies on low-penetrance genes do cite PAFs, referring to the high population burden conferred by the variants in spite of their low relative risks. The PAF of a gene variant integrates any unmeasured gene–gene and gene–environment interactions for the particular study population, which implies that PAF may vary from one population to the next [11]. The variation could be expected to distinguish populations with variable allele frequencies and/or environmental exposures, i.e., those with large differences in cancer incidence. Age structure of the population is important in the presentation of any risk parameters, which has been dealt elsewhere [7]. Suffice to point out that when more than 10% of the women will develop breast cancer (i.e., the cumulative risk is over 10%) any relative risk even for factors causing breast cancer in all women has to be below 10. Most data on carrier frequencies emanate from relatively young populations, where relative risks may exceed 10 but extrapolation to the whole population remains an enigma.

Population attributable fractions (PAFs) can be calculated based on the genotype relative risks of the variants and on their allele frequencies as shown elsewhere [7]. Among the high-penetrance genes, the PAFs for BRCA1 and BRCA2 each are at or above 0.5% in European populations aged up to 70 years [7]; the PAFs would be somewhat lower in the whole population where we could consider around 1.0% a good estimate (Fig. 1). For some of the moderate-penetrance genes, ATM, BRIP1, CHEK2 and PALB2, the data are still limited to single populations [12–16]. For CHEK2*del1100delC and ATM variants the PAF estimates are about 0.5% each; adding up the other CHEK2 variants, BRIP1 and PALB2 mutations the sum PAF would be around 1.5% (Fig. 1). Among low-penetrance alleles, PAF for TGFbeta1 and CASP8 may account for 5.7 and 3.2%, respectively [3]; the five loci described by Easton et al. [4] (close to genes/loci FGFR2, TNRC9, MAP3K1, LSP1, 8q) can be calculated to confer a joint PAF of 36%, assuming independence and multiplicative epistatic interactions; the two loci described by Stacey et al. on chromosomes 2q35 and 16q12 confer PAFs of 5.3 and 7.1%, assuming that estrogen receptor-positive breast cancers accounted for 50% of all breast cancer [5]. Assuming that the low-penetrance loci act independently and multiplicatively, their joint PAF can be estimated at 58% (Fig. 1).

The present calculations are based on the published data on genotype relative risks and frequencies of the variant alleles, both of which may vary according to the populations studied. The exact results depend also on the assumed

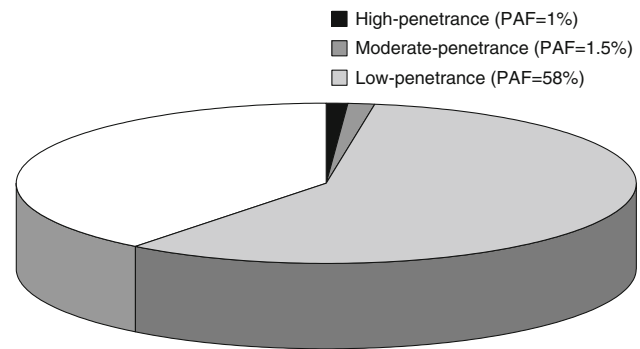


Fig. 1 PAFs for high-, moderate- and low-penetrance variants underlying susceptibility to breast cancer

mode for genotypic and epistatic interactions for which limited data are available. The evidence appears, nevertheless, compelling in pointing to the remarkably high population impacts of the recently described heritable loci compared to the ‘classical’ high-penetrance genes. As it seems now, the genome scans on breast cancer have opened a wide genomic landscape of flat hills which abruptly break off from the few well known mountain ridges. The lack of intermediary peaks has been considered a paradox, which however may be explained by the applied research tools: linkage studies were used to find the high-penetrance genes and genome scans were used to find the low-penetrance variants. By definition, the former detects rare variants of high risk while the latter finds common variants of low risk [11]. We may have missed the intermediary mountains because we have not had the right tools to find them: they are of too low risk to be found in linkage studies and too rare to be found in genome scans. The most feasible way to find them would probably be to focus on relatively rare variants in familial and bilateral breast cancer cases [17–19].

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