EDITORIAL

Breast cancer genetics: the past, present and future

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Patients and doctors have high expectations when it comes to genetics. The expanding knowledge of the human genome in health and disease should result in early identification of individuals at risk and targets for therapy. To date, different methods have been used to identify genetic variants associated with disease, dependent on availability and technical advancement in basic sciences. In the past, large families with a Mendelian inheritance pattern of a specific trait were studied. Hall *et al.* identified that chromosome 17q21 appeared to be the locus of a gene for inherited susceptibility to breast cancer in families with early-onset disease.[1] Genetic analysis yielded a LOD score (logarithm of the likelihood ratio for linkage) of 5.98 for linkage of breast cancer susceptibility to D17S74 in early-onset families and negative LOD scores in families with late-onset disease.[1] Further investigations demonstrated that this region harboured the well-known BRCA1 gene.[2] Family studies were largely abandoned, because large families which facilitate gene discovery are nowadays scarce.

The next step was to test the association of genetic variants in case-control studies. Technically, this was made possible by the Human Genome Project, which increased our knowledge on 'normal' genetic variation.[3] Initially, only a small set of pre-selected candidate genes could be studied. Each variant needed to be typed by hand, which was a laborious process. These candidate genes were carefully selected based on prior knowledge of the disease.

In the current issue of the Netherlands Journal of Medicine, Li *et al.* publish a systemic review and meta-analysis on such a candidate gene for breast cancer: CASP8 -652.[4] In the early 2000s many studies showed that caspases are at the crossroads of immune cell life and death, and their aberrant expressions or activities are associated with many pathological conditions, including cancer. Therefore, variation in this gene was studied in 1K cases and controls.[5] Even though the initial study showed a clear association, following individual studies showed conflicting results. Li *et al.* test the hypothesis that deletions in CASp9 are associated with a reduced risk of breast cancer in the largest study to date: 13,220 cases and 13,750 controls. After combining the data, a specific polymorphism CASP* -652 6N del is associated with a reduced risk (homozygous carriers; R=0.78, 95% CI 0.63-0.95; dominant OR=0.93, 95 % CI 0.88-0.99). They rightfully conclude that large sample studies using standardised unbiased genotyping methods, in homogenous breast cancer patients and well-matched controls, are needed to ultimately lead to a better understanding of the association of CASP8-652N del and breast cancer.

In the present, thanks to technical advancement and the development of DNA chips containing hundreds of thousands of genetic variants, the standards for gene discovery have evolved from candidate gene approaches to unbiased whole genome approaches in the Genome-Wide Association Studies (GWAS). A recent study of 10K breast cancer cases and 12K controls followed by a replication study of 43K cases and 42K controls identified 41 loci associated with breast cancer.[6] In contrast to Li *et al.* the latest GWAS unfortunately no longer demonstrates a clear association between variation in CASP8 and breast cancer. The GWAS studies have the power to detect an association with common variants and disease. The majority of these variants have a small effect on the disease phenotype. Individually, they can therefore not yet be applied to predict breast cancer. However, incorporating these loci into risk models is expected to improve disease prediction. The latest developments are sequencing all protein coding regions of large cohorts of individuals in the hope to identify rare variants with large effects. Incorporating these into models will probably improve them. One should bear in mind that association does not imply causality. In depth sequencing of regions associated with disease should result in the identification of causal variants.

In the future, functional studies are needed to understand, if and through which pathophysiological mechanisms the identified genetic variation result in disease.

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