Initial description of the LD pattern and the haplotypic structure of the BRCA 1 and 2 genes in the German population

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Introduction The "Berlin Center for Hereditary Breast and Ovarian Cancer" as one of twelve centers of the "German Consortium for Hereditary Breast and Ovarian Cancer" (GCHBOC) investigated about 300 German high-risk breast and/or ovarian cancer families for mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 during 1997-2005. We were interested in understanding the linkage disequilibrium (LD) pattern and the haplotypic structure of the BRCA1 and BRCA2 genes among German women who were previously tested by direct sequencing of all exons and exon-flanking intronic regions of both genes.
Material and Methods We estimated haplotype frequencies in the BRCA1 and BRCA2 genes, based on 22 single nucleotide polymorphisms (SNPs) spanning 80.78 kb of the BRCA1 gene and 25 SNPs spanning 83.01kb of the BRCA2 gene. SNPs were genotyped in 172 and 217 investigated index patients, respectively, by direct sequencing. We also assessed the pattern and the extent of LD between the SNPs in BRCA1 and BRCA2 and compared the results to data from the International HapMap project [1]. We further investigated the effect of restricting the analysis to haplotype-tagging SNPs as compared to using the full set of SNPs.
Results Out of five different BRCA1 haplotypes with a frequency of > 5%, two common BRCA1 haplotypes accounted for two thirds of all chromosomes in our collective. In contrast, analysis of BRCA2 haplotypes revealed a higher haplotypic diversity, with the most abundant haplotype accounting for 17%. Haplotype frequency estimates had considerable confidence intervals, making it difficult to draw conclusions from differences between the various data samples. While most haplotype-based and LD-based block methods agreed on a single coherent region of elevated LD that spanned most of BRCA1, BRCA2 showed low levels of LD in general and only a single area of strong LD. Furthermore, an unusual BRCA2 haplotype was detected in a German high-risk breast cancer family. This haplotype is characterized by the loss of a high-LD area in BRCA2 and represents a hemizygous region that results from a disease-causing intragenic deletion.
Discussion While the usefulness of SNP-based haplotype analysis for distinguishing between groups can be questioned due to a number of uncertainties, it might prove to be an effective approach for identifying patient samples with intragenic deletions leading to hemizygosity. Also, our results indicate that results from the HapMap project are not necessarily representative for the German population and caution is needed when extrapolating from the HapMap data to studies with German individuals.

Literatur

[1] The International HapMap Consortium (2003) The International HapMap Project. *Nature* 426:789–796.