

Short tandem repeat polymorphism and cancer risk: influence of laboratory analysis on epidemiologic findings

Abstract:

Short tandem repeats (STR) are common polymorphisms in the genome. The length of STR may influence gene transcription, exhibiting diverse phenotypes. Two STRs, one trinucleotide repeats in the androgen receptor (AR) gene and one dinucleotide repeats in the insulin-like growth factor-I (IGF-I) gene, have been studied for their role in cancer, and the results are conflicting. Although there are many reasons for inconsistent findings, laboratory issues are often overlooked. DNA sizing analysis is regularly used to determine the length of STR, but its analytic validity has not been evaluated in epidemiologic studies. To examine if sizing analysis can reliably determine dinucleotide STR, we compared the method with direct DNA sequencing in analyzing CA repeats in the IGF-I gene in a small case-control study. The study enrolled 75 breast cancer cases and 75 age- and race-matched controls. DNA was extracted from buffy coats and was analyzed for CA repeats by both DNA sizing and direct sequencing. Our comparison indicated that these methods detected the same number of repeats in the short allele but not in the long allele. There was a substantial discrepancy between the methods in determining homozygous alleles. Although the two methods showed <10% of samples having an exact match on the number of repeats in both alleles, both techniques were able to detect a genotype-phenotype correlation and a racial disparity in the genotype. An association between breast cancer risk and IGF-I genotype was found in sequencing analysis but not in sizing analysis. Overall, the comparison suggests that laboratory analysis of dinucleotide STR may not be as reliable as originally thought. This unreliability in STR analysis may result in inconsistent study findings.