

Study of Microsatellites Role in BRCA2 Gene Causing Pancreatic Cancer and Breast Cancer

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Abstract

BRCA2 gene plays an important role in the development of pancreatic cancer. Diabetics may have a slightly increased risk of pancreatic cancer. Previous literature reveals that the Mutations in these genes are also causing the breast cancer. A detailed bioinformatics study of all the known mutations in the BRCA2 gene revealed interesting information. The information of all the experimentally proven mutations were collected and analyzed using bioinformatics tools and software programs. We tried to find out whether the presence of microsatellites or simple sequence repeats in the BRCA2 gene has any significance in the generation of these mutations. Our analysis revealed that there are 161 mutations available (HGMD) in BRCA2 gene under mis-sense/nonsense Category. We report that none of these 161 mutations fall inside the microsatellite tracts and thus indicating no role of microsatellites in BRCA2 gene.

Keywords: Microsatellites; bioinformatics; pancreatic cancer; breast cancer

Introduction

“Microsatellites” are currently one of the most commonly used genetic markers. They are defined as loci (or regions within DNA sequences) where short sequences (1-6bp length per repeat unit) of DNA are repeated in tandem arrays. This means that the sequences are repeated one right after the other. Their high length polymorphism and abundance in all genomes make them the genetic marker of choice for a diverse range of applications spanning linkage analysis and genetic mapping through to forensic and ecological and evolutionary studies (Goldstein and Schlotterer, 1999). The lengths of sequences used most often are di-, tri-, or tetra-nucleotides. Microsatellites have been found in all the known genomes so far and are widely distributed both in coding and non-coding regions (Sreenu, V.B. et al 2006). They are known to be highly polymorphic as a result

of high rate of mutations in the form of increase/decrease of their repeat copy numbers (Jarne, P. and Lagoda, P.J.L. 1996). Increase/decrease of repeat copy numbers in microsatellites in coding regions often lead to shifts in reading frames thereby causing changes in protein products (Li, Y.C. et al. (2004), Sreenu, V.B. et al. (2006)) and in non-coding regions, known to effect the gene regulation (Martin, P. et al. 2005). Mutations occurring at microsatellite loci within or near certain genes have been implicated to be responsible for some human neurodegenerative diseases (Tautz, D. and Schlotterer, C, 1994). Furthermore, microsatellite instability has also been implicated in the induction of cancer (Thibodeau, S.N. et al., 1993). Owing to their high mutability, it is thought that the microsatellites are one of the sources of genetic diversity (Kashi, Y. and King,

| Accession Number | Codon change | Amino acid change | Codon number | Phenotype |
|------------------|--------------|-------------------|--------------|---------------------|
| CM980233 | gTTT-CTT | Phe-Leu | 32 | Breast cancer |
| CM970178 | TAT-TGT | Tyr-Cys | 42 | Breast cancer |
| CM014326 | tGAA-TAA | Glu-Term | 45 | Breast cancer |
| CM011914 | aGAA-TAA | Glu-Term | 49 | Breast cancer |
| CM980234 | AAA-AGA | Lys-Arg | 53 | Breast cancer |
| CM041729 | ACT-ATT | Thr-Ile | 64 | Breast cancer |
| CM980235 | aTTC-CTC | Phe-Leu | 81 | Breast cancer |
| CM040380 | TTA-TGA | Leu-Term | 105 | Breast cancer |
| CM021250 | ATG-ACG | Met-Thr | 192 | Pancreatic cancer |
| CM960192 | TGG-TAG | Trp-Term | 194 | Breast cancer |
| CM980236 | CCA-CGA | Pro-Arg | 201 | Breast cancer |
| CM980237 | GTC-GCC | Val-Ala | 211 | Breast cancer |
| CM980238 | tCCT-TCT | Pro-Ser | 222 | Breast cancer |
| CM042309 | tACT-GCT | Thr-Ala | 225 | Breast cancer |
| CM032200 | TCA-TAA | Ser-Term | 273 | Breast cancer |
| CM984124 | aCAA-TAA | Gln-Term | 321 | Breast cancer |
| CM994736 | AGCa-AGA | Ser-Arg | 326 | Breast cancer |
| CM994284 | cAAG-GAG | Lys-Glu | 327 | Breast cancer |
| CM002750 | aAAT-CAT | Asn-His | 372 | Breast cancer |
| CM021509 | cAAG-TAG | Lys-Term | 385 | Breast cancer |
| CM970179 | TTG-TAG | Leu-Term | 414 | Breast cancer |
| CM004188 | GAA-GGA | Glu-Gly | 462 | Breast cancer |
| CM021955 | tAAG-TAG | Lys-Term | 467 | Breast cancer |
| CM010167 | ATA-ACA | Ile-Thr | 505 | Breast cancer |
| CM980239 | TGTc-TGG | Cys-Trp | 554 | Breast cancer, male |
| CM043454 | TTA-TGA | Leu-Term | 557 | Breast cancer |
| CM043977 | TGGc-TGA | Trp-Term | 563 | Breast cancer |
| CM033756 | cACT-CCT | Thr-Pro | 582 | Breast cancer |
| CM043978 | TCA-TAA | Ser-Term | 611 | Breast cancer |
| CM004714 | ATAa-ATG | Ile-Met | 729 | Breast cancer |
| CM042681 | cATG-GTG | Met-Val | 784 | Breast cancer |
| CM994285 | tGAT-AAT | Asp-Asn | 935 | Breast cancer |
| CM970180 | tAAA-TAA | Lys-Term | 944 | Breast cancer |
| CM040688 | gAAG-TAG | Lys-Term | 1026 | Breast cancer |
| CM043979 | TTA-TGA | Leu-Term | 1053 | Breast cancer |
| CM020102 | TCA-TGA | Ser-Term | 1099 | Breast cancer |

Table 1 : List of Mutations and its corresponding disease Pheno-type collected from HGMDMaterials

D.G., 2006). In the recent times, efforts have also been made to study the possible functional roles of microsatellites in giving rise to certain amount of plasticity and also in the evolution of genomes (Sreenu, V.B. et al. 2006).

Methods

All the experimental proved mutations of the BRCA2 gene, that are falling inside the coding regions and eventually leading to phenotypic differences were collected from the Human Gene Mutation Database (HGMD) (Stenson et al. 2003). Table 1 gives the list of some mutations considered for analysis. The mutations do not include silent mutations, which do not induce any change in the amino acid sequence. The BRCA2 gene and protein sequences were downloaded from National Center for Biotechnology Information (NCBI) (<http://www.ncbi.nlm.nih.gov>) repository. The BRCA2 gene has 2 exons with an intron in between. The coding regions in the gene sequence were extracted using a perl program and submitted to the microsatellite extraction program called IMEx (Imperfect Microsatellite Extractor) (Mudunuri, S.B. and Nagarajaram, H.A. 2007). We used the intermediate version of IMEx-web server (<http://www.cdfd.org.in/imex>) with the default values. The mutations collected are then mapped on to these microsatellite regions.

Result

The Human Genome Mutation Database (HGMD) is used to identify mutations of BRCA2 gene. Interestingly 161 mutations are found. It is observed that none of these mutations fall in the homeodomain region of the microsatellites. This indicates that microsatellites play no role in the mutagenesis of BRCA2 gene.

Conclusion

Microsatellites are known for their higher rate of mutations and are known to be associated with various diseases. So, we analyzed the BRCA2 mutations and their possible association with the microsatellites. The BRCA2 mutations from HGMD database are not mapped on to the microsatellite tracts and the results seem to indicate that microsatellites play an important role in mutagenesis. Extending this work on a large scale by analyzing large number of genes might give a better evidence of the role of microsatellites in generating mutations.

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