ORIGINAL ARTICLE

Population-Specific Genetic Variation of TRAIL in Ovarian Cancer

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ABSTRACT

Objective: Genome-wide, high-throughput technologies have made major advances in understanding the molecular basis of ovarian cancer and contribution of a single genetic variant, multiple genetic variants, and the contribution of cumulative effect of a genetic variant and an environmental factor to the difference in the incidence of disease have been extensively studied. There is a progressive increase in the studies related to TRAIL mediated signaling and it has been reported that there is a highly polymorphic region in the TRAIL promoter with four SNPs located in a 111 base pair (bp) spanning sequence between nucleotides 707 and 597 upstream of the transcriptional start site.

Methodology: A C/T polymorphism at 1595 position in exon 5 of the TRAIL gene was genotyped in a Pakistani Ovarian cancer case-control population including 19 cases and 24 controls using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis.

Results: In the present study, we determined TRAIL 1595 C/T polymorphism in 19 ovarian cancer patients and 24 controls. The results indicated that out of 19 patients 10 (52.6%) were of CT genotype. 6 (31.5%) were homozygous for C and 3 (15.7%) were homozygous for T. Genotyping of age and sex matched controls revealed that out of 24, 9 (37.5%) were of CT genotype. 12 (50%) were CC and 3 (12.5%) were TT.

Conclusion: TRAIL and Death Receptors are components of apoptotic signaling networks, and a better knowledge of how these networks operate is an important step in understanding cancer progression. Our research group is the first to report role of the TRAIL polymorphism at position 1595 in 3'UTR in ovarian cancer risk and progression.

Keywords: Polymorphism, exon, TRAIL

INTRODUCTION

It is encouraging to note that rapidly evolving technologies are generating massive and highly dimensional genetic variation data that allow nearly complete evaluation of genetic variation including both common and rare variants in different populations. TNF-related apoptosis-inducing ligand (TRAIL) was initially identified by its sequence homology with other tumor necrosis factor (TNF) family members and has been shown to induce apoptosis in tumour cells but not in normal cells Farooqi et al, 2011; Farooqi et al, 2013; Allen and El-Deiry, 2012. Laboratory methodologies provide sufficient evidence that SNPs are the most common genetic variations in the human genome. Considerably frequent number of SNPs in the human genome provides highest resolution (in comparison to other genetic markers such as micro-satellites and mini-satellites) and enables basic and clinical scientists to comprehensively characterize the entire human genome. In the past decade, the fields of pharmacogenetics and pharmacogenomics have developed exponentially and paralleled with that has been growing interest in translation of pharmacogenomics research findings into clinical practice. Reconceptualization of phenotype- and genotype-driven studies convincingly reveals a greater level of intricacy, with evidence of incremental dosage effects, gene interaction networks, buffering and modifiers, and position effects. In this preliminary research work we studied germ line mutation in TRAIL gene in ovarian cancer patients.

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MATERIALS AND METHODS

A C/T polymorphism at 1595 position in exon 5 of the TRAIL gene was genotyped in a Pakistani Ovarian cancer case-control population including 19 cases and 24 controls using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis. The 391-bp PCR product was digested by RsaI. The digested PCR products

generated two bands consisting of 59 and 332 bp (C allele) or three bands consisting of 59, 146, and 186bp (T allele).

RESULTS

In the present study, we determined TRAIL 1595 C/T polymorphism in 19 ovarian cancer patients and 24 controls. The results indicated that out of 19 patients 10 (52.6%) were of CT genotype. 6 (31.5%) were homozygous for C and 3 (15.7%) were homozygous for T. Genotyping of age and sex matched controls revealed that out of 24, 9(37.5%) were of CT genotype. 12 50%) were CC and 3(12.5%) were TT. It seems worthwhile to mention that we did not relate genotype with cancer stage although this aspect has previously been addressed. Previously published study highlighted the fact that heterozygous TRAIL CT polymorphism in exon 5 was present in 8.3% of tumour stage III-IV and 48.8% of stage I-II patients Yildiz et al, 2010.

RFLP results of TRAIL gene in ovarian cancer patients

TRAIL Genotypes	**CT**	**CC**	**TT**
	10	6	3
	52.6%	31.5%	15.7%

RFLP results of TRAIL gene in controls

TRAIL Genotypes	**CT**	**CC**	**TT**
	9	12	3
	37.5%	50%	12.5%

DISCUSSION

TRAIL is constitutively expressed on macrophages, T cells, natural killer cells, and dendritic cells and selectively kills transformed cells leaving normal cells intact. It is appropriate to mention that we do not have any information that provides a hint of association of TRAIL and its receptors in inducing different cancers in our local population. We have started with germline mutations in TRAIL and DR4/DR5 and later we aim to screen somatic mutations in cancer tissues. On a similar note patient size is small but gradually we plan to screen larger patient pool and latest statistical analyses to substantiate our findings. Detailed studies are essential to unravel complexity of gene regulation and the functional contribution of each genetic determinant to disease susceptibility or carcinogenesis. These studies should progress in parallel with the use of genetically defined populations to explore how both genetic and environmental factors affect the function of the pathways in individuals with and without disease, and how these determine the risk of carcinogenesis.

REFERENCES

1. Allen JE, El-Deiry WS. Regulation of the human TRAIL gene. Cancer Biol Ther. 2012 Oct;13(12):1143-51
2. Farooqi AA, Mukhtar S, Riaz AM, Waseem S, Minhaj S. Wnt and SHH in prostate cancer: trouble mongers occupy the TRAIL towards apoptosis. Cell Prolif. 2011 Dec;44(6):508-15.
3. Farooqi AA, Nawaz A, Javed Z, Bhatti S, Ismail M. While at Rome miRNA and TRAIL do whatever BCR-ABL commands to do. Arch Immunol Ther Exp (Warsz). 2013 Feb;61(1):59-74.
4. Yildiz Y, Yaylim-Eraltan I, Arikan S, Ergen HA, Küçücük S, Isbir T. Is there any correlation between TNF-related apoptosis-inducing ligand (TRAIL) genetic variants and breast cancer? Arch Med Sci. 2010 Dec;6(6):932-6.