

## Guideline of Tumor Suppressor Genes in Acute Leukemia

Walaa Fikry Elbossaty

Department of Biochemistry, Faculty of Science, Damietta University, Egypt

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### Abstract:

#### Introduction:

Leukaemia is malignancy of the white blood cells. Acute leukaemia revenues the state of growths fast and aggressively, requiring immediate treatment. Acute leukaemia is classified according to the type of white blood cells that are affected. In addition, the rate of infection it can be classified in to acute or chronic state. Although incredible efforts have been made in the identification of susceptible factors of leukemia, the pathogenesis of leukemia is not fully elucidated.

Common fragile sites (CFSs) are large chromosomal regions that are hot-spots for alterations specifically within malignant cells. The three most commonly expressed CFS regions (FRA3B, FRA16D and FRA6E) encompass genes that extent tremendously large genomic regions (FHIT, WWOX and PARK2, respectively), and these genes were established to occupation as essential tumor suppressors. The loss of expression of just FHIT or WWOX has been found to be associated with a worse overall clinical outcome.

There were different causes for induced leukemia one of them genetic abnormalities. There was a big class of genes called tumor suppressor gene any gene mutation in this group lead to development of leukemia. Fragile Histidine Triad and WW-domain oxidoreductase are tumor suppressor genes; they are located on the most important fragile loci FRA3B and FRA16D at chromosome 3p14.2 and 16q23.3 respectively. Any change in gene expressions may be reflecting the presence of malignant tumor. There is no specific serum biochemical marker for detection of leukemias so; this study was planned to determine the prognostic significance of both FHIT and WWOX in acute leukemia...

#### Materials and Methods:

Eighty patients who diagnosed for acute leukemia were investigated for this study. Patient's history included age, gender, clinical manifestation, time of disease discovery, period of fellow up ,length of remission period, treatment protocol have been detected. In addition to, the FHIT and WWOX gene expressions were determined by using QRT-

### Results:

Loss of FHIT expression was demonstrated in 24 (48%) AML patients, in 15(50%) ALL patients and loss of WWOX expression was demonstrated in 25 (50%) AML patients, in 15(50%) all patients. There was statistically significant positive correlation between FHIT and WWOX gene expressions. There were statistically significant correlation between FHIT and WWOX gene expressions and clinical outcome and survival time.

In this study high expression both FHIT and WWOX expressers group showed a statistically higher CR(100%,66.7%,26%) ;(100%, 50%, 18.2%) ,( p =<0.001, p =0.022) in AML,ALL respectively, low relapse (0%,0%,26.1%);(0%,0%,31.8%) (p=0.314, p=0.805) in AML, ALL respectively, low refractory (0%, 0%, 21.7%) ;( 0%, 16.7 %, 59%) (p=0.029, p=0.033) in AML, ALL respectively, low induction death (0%, 33.3%, 56.5%) ;( 0%, 16.7 %, 27.3%) (p=0.015, p=0.041) in AML, ALL respectively and low die rate (12.5%, 66.7%, 91.3%) ;( 9%, 33.3 %, 95.5%) (p =0.292, p =0.121) in AML,ALL respectively when compared with discordant FHIT and WWOX expressers group and low expression both FHIT and WWOX expressers group respectively.

A significantly better OS survival was observed among patients with acute leukemia exhibiting high both FHIT and WWOX gene expression group when compared with discordant FHIT and WWOX expressers group and low expression both FHIT and WWOX expressers group (39.7 , 28.685 , 10.378 ); (42.750 , 31.44 , 13.99 );( p =0.043, p =0.008) in AML ,ALL respectively. These parallels lead us to propose that there is a functional basis for the association of the tumour suppressor genes WWOX and FHIT with the most unstable common chromosomal fragile sites in humans. The presence of these fragile sites confers the potential for DNA damage within the respective genes.

Those cells with a resultant increase in expression of WWOX and/or FHIT therefore have increased resilience to further oxidative stress by virtue of increased ROS. We therefore propose that the common pathways in which WWOX and

FHIT participate form a network of 'front-line' responses to environmental stresses.

## Conclusion:

These results suggest that loss of the normal FHIT function may be involved in the genesis of at least some human leukemias and that low expression of FHIT gene is rather specific and frequent in acute leukemia samples. FHIT expression is an important prognostic factor in AML, ALL patients with normal Karyotyped, and therefore we recommend its incorporation into novel risk-adapted therapeutic strategies to improve the currently.

As far as we can tell, this is the first investigation regarding the role of the WWOX gene in the pathogenesis of human leukemia. Because the loss of WWOX expression is common, involved in the pathogenesis of leukemia and provide new therapeutic opportunities for acute leukemia with the emerging drugs that reverse the cancer associated epigenetic alteration. The present study provides evidence for that WWOX may act as a tumor suppressor gene in acute leukemia, and that it may represent a potential biomarker of poor prognosis and a potential therapeutic target for acute leukemia interven-tion.

The aforementioned findings that WWOX down expression was associated with aggressive tumor progression indicated that its possible prognostic value in AML, ALL patients should be investigated in the present study. A significantly better OS survival was observed among patients with acute leukemia exhibiting high WWOX gene expression.

In the current study acute leukemia and healthy control cases, revealed statistically a highly significant correlation between the two studied markers (FHIT and WWOX genes) according to Spearman's Correlation. These results support the concept that both markers are tumor suppressor and reduce in acute leukemia cases.

Therefore, we speculate that statistically significant difference between FHIT and WWOX among groups of AML, ALL and healthy control cases observed in this study suggest their close and synergistic, cooperation and co activation in the malignant potential of leukogenesis and can be used as early diagnostic markers for evaluating these type of blood cancer. The combination between the both FHIT and WWOX gene expressions consider as important independent prognostic factor for acute leukemia and the both play important role in disease prognosis.