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The identification of the de novo variation p.Gly70Ser of WT1 gene: a possible genetic contribute to the clinical phenotype

Padula MC¹, Salvia I¹, Mangieri MA¹, Busilacchi E², Martelli G¹, Saraceni F² and Olivieri A²

¹Department of Science, University of Basilicata, Potenza, Viale dell'Ateneo Lucano, 10, 85100, Italy

²Clinic of Hematology, Hospital-University Company "Ospedali Riuniti di Ancona", Ancona, Via Conca, 60126, Italy

Introduction. The Wilms' tumor 1 gene (WT1) is related to several hematopoietic malignancies, including acute myeloid leukemia (AML) [1]. It encodes a 49-52 kDa protein with both oncosuppressor and oncogene roles [2]. WT1 mutational state as AML molecular marker is an attractive research topic for better clarify the gene role in cancer progression [3, 4]. The aim of our study was to investigate the genetic contribution to the AML clinical phenotype searching for WT1 SNPs with functional impact on gene function.

Patient and methods. A 80 year-old male was recruited from the Clinic of Hematology, Hospital-University Company "Ospedali Riuniti" in Ancona (Italy). Genomic DNA was extracted from patient whole blood by using standard procedures and spectrophotometrically quantified. The whole WT1 gene structure (coding region, exon-intron boundaries, 5' and 3' Untranslated Regions) has been screened by means of PCR amplification (with specific primers) and direct sequencing. Bioinformatics software (BlastN and Mutation Surveyor) were used for DNA variant analysis compared to the gene RefSeq (NG_009272.1). *In silico* investigations were also performed for predicting: RNA fold (RNAfold server), variant deleteriousness (Polyphen2 server), 2D protein structure (Hydrophobic Cluster Analysis, Mobyle server) and 3D protein structure (Phyre2 server).

Results. By investigating the mutational state of WT1 gene, as well as minor or known mutations, we found a novel variant, a substitution G>A (NG_009272.1:g.5404G>A, HGSV nomenclature) in homozygosity state. It is responsible, at protein level, for the change p.G70S (NP_000369.3:p.Gly70Ser; HGSV nomenclature) that resides within the WT1 repression domain. Polyphen2 server showed the deleteriousness of the de novo variant. The mRNA folding process occurs in a non-canonical way. The hydrophobic cluster and 3D protein structure were significantly affected by the presence of the variation, that is responsible for the loss of the alpha-helical structure.

Conclusion. The molecular findings suggest a functional impairment of WT1 protein that could affect its biological regulatory role. The novel variation could be related to the poor prognosis and provides a significant background for a molecularly-based risk assessment and a subsequent treatment stratification.

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Biography

Experienced biotechnologist with certifications, 4-5 years experience as a senior Microbiologist and Specialty Service Director of Iranian Biological Resource Center (IBRC) under the authority of Academic Center for Education, Culture and Research (ACECR) and additional 5 years working as Microbiology technologist at medical laboratory in addition to premier research background and a MSc. degree in Microbiology from Karaj Islamic Azad University (IAU).

mcpadula25@gmail.com