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A novel DNMT3A gene variation within SAM domain: implications for the clinical henotype

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INTRODUCTION. DNA methylation is a well-known epigenetic modification. The relation between DNA methylation and gene transcription has been studied in the last years: several evidences that developmental transcription factors affect DNA methylation by regulating the DNA methyltransferases (DNMTs) expression were reported1-4. Gene hypermethylation modulates significant development mechanisms but is also a common signature of cancer cells3. Gene variations of methylation expression pattern have been identified in different types of cancers, mainly hematological tumors, such as acute myeloid leukemia (AML)5. In particular, mutations in DNA methyltransferase 3A (DNMT3A) gene were reported in AML: approximately 20% AML patients showed DNMT3A gene mutations; a poor clinical outcome was observed when these variations occur6.

PAZIENTS AND METHODS. We reported a clinical case: the patient W17 is a 80 years-old male belonging to an Italian cohort recruited from the Clinic of Hematology of "Ospedali Riuniti" in Ancona (Italy). Proband genomic DNA was isolated at AML onset. PCR amplification was performed with specific primers (designed by means of NCBI Primer-Blast for detecting DNMT3A coding region, exon-intron boundaries, 5' and 3'Untranslated Regions) and Ampli Taq GOLD® DNAPolymerase kit (Applied Biosystem) according to the manufacturer's instructions. Amplification products were analyzed by 1.5% agarose gel electrophoresis, isolated and sequenced. BlastN algorithm (NCBI database) and Mutation Surveyor software were interrogated for *in silico* similarity analysis. If a novel mutation was identified, it was confirmed by a second PCR step. We used Polyphen 2 software for predicting the functional impact of gene variants and Mobile software for performing the Hydrophobic Cluster Analysis (HCA).

RESULTS. The mutation analysis of DNMT3A gene underlined a novel variation in our proband genome. This mutation is a T>A base substitution, within exon 20 and was found in heterozygosity state (NG_029465.1:g.106007T>A, HGSV nomenclature). It is responsible for the p.V687D substitution (NP_072046:p.Val687Asp) at protein level. The change resides within the oligomerization SAM (S-adenosyl-methionine) domain of the enzyme. In addition the mutation is classified as highly impactful when we bioinformatically investigated its pathogenicity. The substitution resulted in a significant change in 2D structure (HLA cluster). This aspect could be related to the different aminoacidic chemical properties: Valine is an aliphatic aminoacid while the aspartic acid is negatively charged aminoacid. The chemical difference could significantly affect the protein function with possible clinical implications.

CONCLUSIONS. The presence of the mutation within the SAM oligomerization site resulted in a conformational change of the enzyme which methyltransferase activity. This activity could be reduced by approximately 50% compared to the wild-type enzyme. We speculated about a possible correlation between the presence of our de novo gene variant and the patient clinical phenotype. This aspect is to be validated in further investigations.

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).

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