الاستهلال

بسم الله الرحمن الرحيم

قال الله تعالى: {وَلَقَدْ خَلَقْنَا الإِنسَانَ مِنْ سُلالَةٍ مِنْ طِينٍ * ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَكِينٍ * ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ}

[المؤمنون: 12-14].

صدق الله العظيم

Dedication

To my Lovely mother, to my father,

To my brothers and sisters

To my teachers at Omdurman Ahlia University
To my colleagues and friends

To all who have lent me a hand

to make the accomplishment

of this work possible

I dedicate this work

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Abstract

This study was cross sectional hospital based to detect the mutation of WT1 gene in Sudanese patients with acute myeloid leukemia, this study was carried out in Radiation and Isotopes Center in Khartoum ,during the period March 2012 to Feb Dec 2013.

Fifty one Sudanese patients with Acute Myeloid Leukemia were informed about the study and the agreement for participation was obtained, twenty six were male and twenty five were female, their ages range between 10 – 70 years old.

5.0 ml of a venous blood were collected in Ethylene Diamine Tetra Acetic acid container, Deoxyribonucleic Acid extraction was done in all patient samples using the salting out method and the quality of extracted DNA were checked on 1% agrose gel by electrophoresis, and then Polymerase Chain Reaction amplification for exon 7 of Williams's tumor 1 gene was done using the specific primers from the published data and the Polymerase Chain Reaction product was 214 bp. For mutation detection restriction fragment length polymorphism was done in all Polymerase Chain Reaction products from the patient samples using the restriction enzyme AflIII.

The mean age of study population was (2.51), and tribal group distribution among the study population were 38 (74.5%) from Afro Asiatic, 3 (5.9%) from Nilo Saharan and 10 (19.6%) from Niger Kordofanian tribal group. genotyping distribution among the study population were 27 (52.9%) were normal (A/A) of Williams's tumor1 mutation, 22 (43.1%) were heterozygous (A/G) of Williams's tumor 1 gene mutation and only 2 (3.9%) of patients were homozygous (G/G) of Williams's tumor 1 gene mutation

In this study we have found the mutation of Williams's tumor 1 gene in 24 of 51 (47.1%), Acute Myeloid Leukemia cases, This mutation frequency is not equivalent to the previous studies of Williams's tumor 1 gene mutation in Acute Myeloid Leukemia, Subsequent studies revealed that Williams's tumor 1 is mutant in approximately 10 - 15% of primary.

In conclusion, the result suggest a possible role of Williams's tumor 1 gene mutation in the development of Acute Myeloid Leukemia in Sudanese and that is because of the heterozygous nature of the mutation , this gene act as an oncogene that inherited as dominant allele (only one mutant allele could causes the disease).

ملخص الدراسة

هذه الدراسة تعتبر دراسة مقطعية للكشف عن الطفرة الجينية لجين ورم وليام واحد لدي السودانيين المصابين بمرض ابيضاض الدم الحاد ، اجريت هذه الدراسة بالمركز القومي للعلاج بالاشعة بالخرطوم في الفترة بين مارس 2012م الي فبراير ديسمبر 2013م .

تضمنت الدراسة واحد وخمسون سوداني مريض بداء ابيضاض الدم الحاد ، تم اعلامهم واخذ موافقتهم كتابيا للمشاركة بالبحث ، كان منهم 26 ذكر و25 انتي وتراوحت اعمارهم بين 10 الي 70 سنة.

تم سحب 5 مل عينة دم وريدية وتم وضعها في انبوب EDTA كمانع تجلط ، تم عمل استخلاص للحمض النووي من جميع عينات المرضي باستخدام طريقة salting out وتم التاكد من نوعية الحمض النووي المستخلص باستخدام عملية الفصل الكهربائي للحمض النووي باستخدام تركيز جل 1%، بعدها تم عمل سلسلة تفاعل البلمرة للحمض النووي المستخلص وذلك لمضاعفة المنطقة 7 من جين ورم وليام واحد وذلك باستخدام الاشعال المخصصة للجين والتي تم نشرها بالاوراق العلمية المعتمده، بعدها تم عمل تحليل تقييد جزء من طول تعدد الاشكال وذلك للكشف عن الطفرة الجينية باستخدام الانزيم المقيد AflIII .

بلغ متوسط اعمار المرضي المشاركين بالدراسة (2,51) وبلغ توزيع العرق الجنسي بينهم 38 (74,5%) افارقة اسيويين ، 3 (5,9%) نيليين صحراويين و 27 (52,9%) زنوج كردفانيين.

بلغت نسبة النمط الجيني بين المرضي المشاركين بالدراسة 27 (52,9%) طبيعين يحملون النط الجيني (A/A) ، 22 (43,1%) غير طبيعين مخالفين يحملون النط الجيني (A/G) و فقط 2 (3,9%) غير طبيعين متجانسين يحملون النط الجيني (G/G) .

في هذه الدراسة وجد تكرار الطفرة الجينية لدي السودانيين المصابين بمرض ابيضاض الدم الحاد في 24 مريض من جملة 51 وذلك بنسبة (47,1%) وهذا التكرار في الطفرة الجنية لا يتطابق مع الدراسات السابقة التي اجريت حيث توصلت الدراسات التي اجريت الي ان نسبة الطفرة الجنية لدي المصابين بمرض ابيضاض الدم الحاد تتراوح بين 10 – 15 % .

كخلاصة وبناءا علي ما توصلت اليه الدراسة ، اقترحت الدراسة ان وجود الطفرة الجينية لجين ورم ويليام واحد لدي السودانيين المصابين بمرض ابيضاض الدم الحاد قد يكون له دور في تطور وحدوث مرض ابيضاض الدم الحاد في السودانيين وذلك لطبيعة التخالف الجيني في الطفرة الجينية، كما اقترحت الدراسة ايضا أن هذا الجين قد يعمل كجين مسرطن ويورث بصفة جينية سائده، حيث ان وجود اليل واحد مريض قد يكون كاف لحدوث المرض.

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Abbreviations

AML	Acute Myeloid Leukemia
ALL	Acute Lymphoblastic Leukemia
ATRA	All-Trans – Retinoic Acid
APL	Acute Promyelocytic Leukemia
BAALC	Brain and Acute Leukemia, Cytoplasmic
BFU-E	Bersa Forming Unit Erythroid
CML	Chronic Myloid Leukemia
CEBPA	C/ Enhancer Binding protein alpha
CFU-GM	Colony Forming unit – Granulocytes , Monocytes
CFU-GEMM	Colony Forming unit – Granulocytes , Eosinophils, Monocytes, Megakaryocytes .
CR	Complete Remission
DNA	Deoxyribonucleic acid
DIC	Disseminated intravascular coagulation
EGFR	Epithelial Growth Factor Receptor
EDTA	Ethylene Diamine Tetra Acetic Acid
FAB	French American British
IV	Inta Venous
ITDs	Internal tendem duplications
MDS	Myelo Dysplastic Syndrome
NPMI	National patients Master index
PCR	Polymerase Chain Reaction
PBS	Phosphate Buffer Saline.

RFLP	Restriction Fragment Length Polymprphism
RNA	Ribo Nucleic Acid
TBE	Tri Boric acid EDTA
WHO	World Health organization
WT1	Williams tumors one