Polymorphism in Genes Involved in Homologous Recombination Repair of DNA as Risk Factors for Development of Acute Myeloid Leukemia

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LIST OF ABBREVIATIONS

A: Adenin
ADCC: antibody-dependent cell-mediated cytotoxicity
ALL: Acute Lymphoblastic Leukemia
AML: Acute Myeloid Leukemia
Ang-1,2: Angiopoietins 1,2
APL: Acute Promyelocytic Leukemia
APMF: Acute panmyelosis with myelofibrosis
AT: Ataxia telangiectasia
ATM: Ataxia-telangiectasia mutated
ATP: adenosine 5'-triphosphate
ATR: Attenuated Total Reflection
ATRA: all-trans-retinoic acid
BER: Base excision repair
BLM: Bloom Syndrome
BM: Bone Marrow
BRCA1, 2: Breast Cancer 1 & 2 genes
BRCT: BRCA1 C Terminus domain
C: Cytosin
CA: chromosomal aberrations
CBF: Core Binding Factor
CD: Cluster of Differentiation
CDC: complement-dependent cytotoxicity
CIMF: Chronic Idiopathic Myelofibrosis
CML: Chronic Myeloid Leukemia
CNS: Central Nervous System
CSF: Cerebro Spinal Fluid
Del: deletion
DIC: Disseminated Intravascular Coagulation
DNA: Deoxy-ribose Nucleic Acid
DSB: Double Strand Break
EMD: Extramedulary disease
ES: emberyonic stem cells
FAB: French-American-British
FANCD2: Fanconi Anemia Complementation group D2
FISH: Florescence In-Situ Hybridization
FTI: Fanesyl Transferase Inhibitors
G: Guanine
GSTM1: glutathione S-transferase M1
GVHD: graft-versus-host disease
H2AX: H2A histone family, member X
HLA: Human Leukocyte Antigen
HR: Homologous Recombination

HUS1: Hydroxyurea-sensitive 1
Inv: inversion
IR: Ionizing Radiation
LDH: lactate dehydrogenase
LIG4: Ligase IV
MDC1: Mediator of DNA damage checkpoint protein 1
MDS: Myelodysplastic Syndrome
Met: Methionin
MGMT: methyl guanine methyl transferase
MLH1: Homolog of MutL of E. coli 1
MLL: Muti-Lineage Leukemia
MMR: Mismatch repair
MND1: Meiotic Nuclear Division 1
MPO: Myelo-Per-Oxidase
MRE11: Meiotic Recombination11
mRNA: messenger Ribose Nucleic Acid
MSH2: Homolog of MutS of E. COLI, 2;
NBS1: Nijmegen Breakage Syndrome 1
NER: Nucleotide excision repair
NHEJ: non-homologous end joining
NOC: not otherwise categorized
NRP-1: Neuropilin-1
NSE: Non Specific Estrase
PAS: Periodic acid Schiff
PB: Peripheral Blood
PBL: peripheral blood lymphocytes
PCC: premature chromosome condensation
PCR: Polymerase Chain Reaction
PLZF: promyelocytic leukemia zinc finger
PML: Pro-Myelocytic Leukemia
RAD1, 9, 17: Homolog of S. Pombe genes,
RAD50: Homolog of S. cerevisiae RAD50
RAD51: a homolog of RecA of E. coli
RARalpha: Retinioc Acid Receptor alpha
RFLP: restriction fragment length polymorphism
RT-PCR: Reversed Transcription-PCR
sAML: secondary AML
SBB: Sudan Black B
SMC1: Structural Maintenance of Chromosome 1
SNP: single nucleotide polymorphism
SOD1: superoxide dismutase 1
SSB: Single Strand Break
STR: Short tandem repeat
T: Thymin
t: translocation

t-AML: therapy related AML
tdt: Terminal deoxynucleotidyl transferase
Thr: Therionin
t-MDS: therapy related MDS
TNF: tumor necrosis factor
TP53: Tumor Protein p53
U: uracil
UV: ultra-violet
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor
WHO: World Health Organization
WRN: Werner Syndrome
XN: xanthohumol
XRCC3: X-ray cross-complementing 3

Abstract

Key Words:
Acute Myeloid Leukemia, Repair Genes, RAD51, XRCC3, Polymorphism.

Objectives:
To determine whether polymorphism in RAD51 and XRCC3 repair genes have an effect on the incidence of AML.

Methods:
PCR-RFLP was used to determine the frequency of the two genes polymorphisms among 40 cases and 20 controls.

Results:
In our study we investigated 40 cases of AML and 20 controls for the polymorphism in 2 DNA homologous recombination repair genes – RAD51 and XRCC3. We found that - regarding RAD51 gene polymorphism - among the cases there were 32 cases with positive expression of the polymorphic gene and only 8 cases with negative expression. While in controls we found only one candidate with positive expression of the same polymorphism. Regarding XRCC3 gene polymorphism; we found that among the cases there were18 cases with positive expression of the polymorphic gene and 22 cases with negative expression of this polymorphism. And among the controls there were 8 candidates with positive expression of the polymorphic gene and 12 candidates with negative expression of the polymorphic gene.

Conclusion:
Our results suggest a strong correlation between the presence of polymorphic RAD51-G135C allele and the incidence of AML.

Introduction and Aim of the Work

There is an ongoing debate about genes and environment, their interactions, and the extent of their relative impact on life and death. However, most common diseases involve not only discrete genetic and environmental causes, but also interactions between the two **(Marcus et al., 2000)**. Although any two unrelated people share about 99.9% of their DNA sequences, the remaining 0.1% is important because it contains the genetic variant that influence how people differ in their risk of disease or their response to drugs and environmental exposures. Discovering the DNA sequence variant that contribute to common disease risk offers one of the best opportunities to understand the complex causes of disease in humans.

In a few cases single genes may have a high impact on the life and death of humans. These are major genes that have been strongly linked to specific diseases and affect families where a mutated variant of such a disease gene is inherited. For example, inherited mutations of the BRCA1 gene are responsible for approximately 40-45% of hereditary breast cancers. However, major, heritable disease genes are uncommon in the general population, and in fact only 2-3% of the total number of breast cancer cases is due to BRCA1 mutation, since this gene is rarely mutated in sporadic cancers **(Rosen et al., 2003).**

Much more common are variants of genes, termed polymorphism, which influence various metabolic processes or our susceptibility to different types of environmental exposure. The genetic polymorphisms that may have impact on our susceptibility to environmental exposures

are found among others, in genes that affect the metabolism of substances and toxins that enters the body and among genes that are important for the repair of genetic damage, which arises in the genome after exposure to genotoxic agents. These genetic polymorphisms will not modify an individual's risk of developing disease by themselves, but rather modify the effect of the exposure and the damage. The importance of low-penetrance polymorphisms depends on exposure. If there is no exposure that could be associated to the polymorphism in question, the possible difference in susceptibility of the alleles is less important, and the disease risk of the individual will not be affected **(www.hapmap.org).**

Acute myeloid leukemia (AML) is a clonal hemopoietic disorder that is frequently associated with genetic instability characterized by a diversity of chromosomal and molecular changes. Most cases of AML arise *de novo*; however, ~10–20% of all cases of AML arise after exposure to chemotherapy or radiotherapy after the treatment of a primary malignancy [therapy-related AML (t-AML); **(Pedersen-Bjergaard et al., 2002).**

DNA is at constant risk from damage from both endogenous and exogenous sources. A large number of highly complex mechanisms have evolved to protect DNA from damage including DNA repair pathways and systems that protect against oxidative stress and other damaging agents. These pathways play a vital role in maintaining genetic integrity. The ability of an individual to prevent and repair damage is genetically determined and is the result of combinations of multiple genes that may display subtle differences in their activity **(Knudsen et al., 2001).**