UNIVERSITI PUTRA MALAYSIA

MICROARRAY-BASED GENOMIC ANALYSIS IDENTIFIES GERMLINE AND SOMATIC COPY NUMBER VARIANTS AND LOSS OF HETEROZYGOSITY IN ACUTE MYELOID LEUKAEMIA

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November 2015

Chair : Sabariah Md Noor, PhD
Faculty : Medicine and Health Sciences

Acute myeloid leukaemia (AML) is characterized by the overproduction of immature myeloid cells that accumulate in blood and bone marrow. While the specific cause of AML is usually unknown, several factors including chromosomal aberrations and genetic mutations have been implicated in the pathogenesis of this aggressive disease. Integration of genetic findings and clinicopathological information is crucial in establishing the diagnosis, prognosis and determining the therapeutic approach in the management of AML patients. The AML classification has evolved from morphology to cytogenetics/molecular genetics-based findings in recent years. Cytogenetic information is important in the detection of chromosomal abnormalities and has provided the framework for the diagnosis and risk-stratification in AML over the past decade. However, conventional cytogenetics is a technically demanding method. The success rate of chromosomal analysis is largely dependent on the availability of optimal and viable cells for culturing and the expertise with experience in identifying chromosomal aberrations at a limited resolution. Insights into molecular karyotyping using comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays enable the identification of copy number variations (CNVs) at a higher resolution and facilitate the detection of copy neutral loss of heterozygosity (CN-LOH) otherwise undetectable by conventional cytogenetics. The applicability of a customised CGH+SNP 180K DNA microarray with additional additional custom probes for 49 genes; every exon of eleven of these genes (TP53, DNMT3A, TET2, ASXL1, MLL, IKZF1, PAX5, EZH2, FLT3, NOTCH1 and ATM) was covered in the diagnostic evaluation of AML was assessed in this study. Paired tumour and germline (remission sample obtained from the same patient after induction) DNA were used to delineate germline variants in 41 AML samples. The prognosis based on karyotyping and molecular genetics was correlated with demographic (age, gender, ethnicity) and laboratory findings (WBC, aberrant antigen expression of CD2, CD4, CD7, CD19 and CD56). After comparing the tumour versus germline DNA, a total of 55 imbalances (n 5-10 MB = 21, n 10-20 MB = 8 and n >20 MB = 26) were identified. Gains were most common in chromosome 4 (26.7%) whereas losses were most frequent in chromosome 7 (28.6%) and X (25.0%). CN-LOH was mostly seen in chromosome 4 (75.0%). Excellent agreements between the karyotype and CGH+SNP analyses were observed in 20 cases, with CGH+SNP analyses providing more precise breakpoint definition. Karyotype was not in agreement with CGH+SNP in 13 cases. In another three cases,

array CGH+SNP detected aberrations which were missed by conventional karyotyping. Translocations were not detected by CGH+SNP in six cases. Correlation between prognosis on karyotyping and molecular genetics based on the clinical and laboratory findings showed statistically significant association between CD19 expression and a favourable prognosis. Statistically significant differences were observed between genders ($P < 0.05$ by Fisher's exact test); females had a more favourable prognosis compared to males. Chromosomal abnormalities with breakpoint coordinates were identified more accurately as compared to conventional cytogenetics with the use of the combined array CGH+SNP platform in this study. In summary, a combined platform of CGH+SNP provides invaluable insights into the elucidation of large spectrum of genomic aberrations in AML which may have prognostic implications.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

PENEMUAN VARIAN *COPY NUMBER* DAN KEHILANGAN *HETEROZYGOSITY* GERMA DAN SOMATIK BAGI LEUKEMIA MYELOID AKUT MELALUI ANALISIS GENOMIK BERASASKAN MIKROARRAY

Oleh

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Leukemia myeloid akut (AML) dicirikan oleh pengumpulan sel-sel myeloid yang tidak matang di dalam darah dan sum-sum tulang. Walaupun sebab khusus untuk AML kebanyakannya tidak diketahui, beberapa faktor seperti aberasi kromosom dan mutasi genetik dikaitkan dengan patogenesis penyakit agresif ini. Integrasi maklumat genetik dan klinikopatologikal adalah penting untuk membuat diagnosis, prognosis dan penentuan hala tuju rawatan terapeutik pesakit AML. Klasifikasi AML telah berevolusi daripada morfologi kepada berdasarkan sitogenetik dan genetik molekular sejak beberapa tahun kebelakangan ini. Maklumat sitogenetik adalah penting dalam pengesanan keabnormalan kromosom dan telah menjadi kerangka bagi diagnosis dan stratifikasi risiko AML sejak sedekad yang lalu. Walau bagaimanapun, teknik sitogenetik komvensional adalah rumit dan kadar kejayaan analisis kromosom bergantung kepada sel hidup yang optimum untuk pengkulturan serta memerlukan kemahiran yang tinggi dalam pengesanan aberasi kromosom pada resolusi yang terhad.Kariotip molekular menggunakan kaedah *comparative genomic hybridization* (CGH) dan *single nucleotide polymorphism* (SNP) membolehkan identifikasi *copy number variations* (CNVs) pada resolusi yang lebih tinggi dan membantu pengesanan of *copy neutral loss of heterozygosity* (CN-LOH) yang tidak dapat dikesan melalui kaedah sitogenetik konvensional. Penggunaan gabungan CGH+SNP 180K DNA mikroarray yang diubahsuai dgn tambahan 49 gen yang merangkumi sebelas gen setiap exon (TP53, DNMT3A, TET2, ASXL1, MLL, IKZF1, PAX5, EZH2, FLT3, NOTCH1 dan ATM) untuk evaluasi diagnostik AML telah dikaji. DNA tumor and germline (sampel remission yang diperoleh daripada pesakit yang sama setelah induksi) dianalisis secara berpasangan untuk membezakan varian germline di dalam 41 sampel pesakit AML.Prognosis berdasarkan kariotip dan genetik molekular dikorelasi dgn maklumat klinikal (umur, jantina and kumpulan etnik) serta penemuan makmal (bilangan sel darah putih, aberasi antigen CD2,CD4, CD7, CD19 dan CD56). Setelah membandingkan DNA tumor dengan germline, sebanyak 55 ketidakseimbangan dikesan (n 5-10 MB = 21, n 10-20 MB = 8 and n >20 MB = 26). Penambahan paling banyak berlaku pada kromosom 4 (26.7%) manakala kehilangan paling banyak didapati pada kromosom 7 (28.6%) dan X (25.0%). CN-LOH paling kerap dilihat pada kromosom 4 (75.0%). Penemuan kariotip dan CGH+SNP adalah bertepatan di dalam 20 kes, di mana CGH+SNP menunjukan breakpoint yang lebih tepat. Penemuan kariotip dan CGH+SNP tidak bertepatan di dalam 13 kes. Array CGH+SNP telah

menunjukkan aberasi pada tiga kes yang tidak dapat dikesan menggunakan kariotip konvensional. Seperti yang sedia maklum, translokasi tidak dapat dikesan mengunakan CGH+SNP seperti yang dilihat berlaku ke atas enam kes. Korelasi telahan berdasarkan kariotip dan genetik molekular dengan penemuan klinikal dan makmal menunjukkan hubungan yang signifikan secara statistik di antara expresi CD19 dan kumpulan telahan memuaskan. Perbezaan signifikan secara statistik dilihat di antara jantina (($P < 0.05$ by ujian Fisher's exact); perempuan lebih banyak di kumpulan telahan memuaskan manakala lelaki lebih banyak di kumpulan telahan pertengahan. Keabnormalan kromosom dengan koordinat yang lebih tepat telah berjaya dikesan menggunakan gabungan array CGH+SNP di dalam kajian ini. Kesimpulannya, gabungan array CGH+SNP memberikan pencerahan untuk merungkai spektrum aberasi genomik AML yang berkemungkinan memberikan implikasi terhadap prognosis.

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I certify that a Thesis Examination Committee has met on 16 November 2015 to conduct the final examination of A Angeli a/p Ambayya @ Ampiah on her thesis entitled "Microarray-Based Genomic Analysis Identifies Germline and Somatic Copy Number Variants and Loss of Heterozygosity in Acute Myeloid Leukaemia" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS

A	Adenine
aCGH	array CGH
ACMG	American College of Medical Genetics
ADM-2	Aberration Detection Method-2
AML	Acute myeloid leukaemia
AML	Acute myeloid leukaemia
AML M0	Undifferentiated acute myeloblastic leukemia
AML M1	Acute myeloblastic leukemia with minimal maturation
AML M2	Acute myeloblastic leukemia with maturation
AML M3	Acute promyelocytic leukemia (APL)
AML M4	Acute myelomonocytic leukemia
AML M5	Acute monocytic leukemia
AML M6	Acute erythroid leukemia
AML M7	Acute megakaryoblastic leukemia
AML-NK	Normal karyotype AML
AvgCGHLR	Average CGH log ratio
BAC	Bacterial artificial chromosomes
BM	Bone marrow
C	Cytosine
CD	Cluster of differentiation
CGH	Comparative genomic hybridization
ChIP	Chromatin ImmunoPrecipitation
Chr	Chromosome
CN	Copy number
CN-LOH	Copy neutral loss of heterozygosity
CNV	copy number variation
CR	Complete remission
Cy3	Cyanine 3-dUTP
Cy5	Cyanine 5-dUTP
dCTP	dCTP-coupled fluorophores with dUTP-c
DFS	disease-free survival
DFS	Disease-free survival
DGV	Database of Genomic Variants

DIC	disseminated intravascular coagulation
DLRSD	Derivative Log2 Ratio Standard Deviation
DNA	Deoxyribonucleic acid
dUTP	Deoxyuridine triphosphate
FFPE	Formalin fixed paraffin embedded
FISH	Fluorescence in situ Hybridization
G	Guanine
gDNA	gDNA
GRCh37	Genome Reference Consortium 37
HSC	Haematopoietic stem cell
ISCN	International System for Human Cytogenetic Nomenclature
kb	kilobase
LSC	Leukaemic stem cells
Mb	Megabase
MDS	Myelodysplastic syndrome
miRNA	micro RNA
MLPA	Multiplex ligation-dependent probe amplification
MPO	Myeloperoxidase
MRD	Minimal residual disease
NSE	Non-specific esterase
OS	Overall survival
PAC	P1-derived artificial chromosomes
PAS	Periodic acid Schiff
PB	Peripheral Blood
PCR	Polymerase chain reaction
QC	Quality control
qPCR	quantitative PCR
RT-PCR	Reverse transcription polymerase chain reaction
SBB	Sudan Black B
SEER	Surveillance Epidemiology and End Results
SNP	Single nucleotide polymorphism
SNP-A	SNP arrays
SPSS	Statistical Package of Social Science
T	Thymine
tCGH	Translocation comparative genomic hybridization
UCSC	University of California, Santa Cruz

UK	United Kingdom
UPD	Uniparental disomy
US	United States
WBC	White blood cell
WHO	World Health Organization
YAC	Yeast artificial chromosome

CHAPTER 1

INTRODUCTION

Acute myeloid leukaemia (AML) is a heterogeneous malignant haematopoietic disorder that is characterized by an increase in immature myeloid cells. It is a result of an arrest of normal cell differentiation in the bone marrow. AML is also known as a disease marked by heterogeneity in diagnosis, classification, response to therapy and survival. Recent insights into the genomic landscapes of AML have led to tremendous advancement in understanding the molecular pathogenesis of this disease. Currently, the state-of-the-art in the diagnosis of AML relies on the integration of clinicopathological findings which include morphologic assessment, immunophenotyping analysis, and genetic studies.

Over the past decade, karyotyping of a minimum of 20 metaphase cells has been considered imperative in the classification and prognostication of AML (Simons et al., 2012). Karyotypically, AML can be stratified into three risk based categories: favourable, intermediate and unfavourable based on specific genetic abnormalities detected by conventional cytogenetics and/or fluorescence in situ hybridization (FISH) (Foran, 2010; Kadia et al., 2014). Cytogenetic information is crucial in identifying translocations, inversions, duplications, deletions and aneuploidies in order to establish diagnosis, prognosis and adjusting specific therapies (Akagi et al., 2009; Le Scouarnec & Gribble, 2011).

Despite providing a genome-wide chromosomal assessment, there are several drawbacks in conventional cytogenetics, in terms of sampling and technical issues. The major issue is the requirement of viable cells that necessitates proper and expedited sample processing. Thus sample quality is critical for this method. Bone marrow is preferable to peripheral blood and the first draw of marrow is recommended whenever possible for karyotyping, Peripheral blood may only yield informative result if the blast counts are higher than 10-20 %. The challenges also lie in dissecting the complex genetic changes due to poor chromosome morphology and indistinct banding. Careful selection of the best metaphases on a slide is likely to bias the analysis towards cells with a normal karyotype and subsequently missing the abnormal clone(s) which could be potentially important contributor to AML pathogenesis (Maciejewski et al., 2009; Vermeesch et al, 2012; Simons et al., 2012).

The accuracy of karyotyping is largely dependent on the number of metaphase and chromosomal banding resolution. Optimal analysis is not possible for the cases with poor metaphases as the location of the chromosomal lesion cannot be clearly defined resulting in underestimation of the degree of chromosomal changes.
Next, conventional cytogenetics require intricate and laborious procedures which involve cell cultures that are tailored to specific cell types. It is also technically demanding as leukaemic cells react differently to various stimuli and this requires more

than one culture. This is due to the varied sensitivity of tumour cells to culture conditions and synchronization procedures. In addition, neoplastic cells are often affected by low mitotic index caused by altered cell kinetics. Leukaemic blast are inclined to undergo apoptosis in culture thus hampering efforts to elucidate chromosomal aberrations. Expertise and meticulous observation are needed to distinguish various random losses from actual aberrations due to technical issues in sample processing (Maciejewski et al., 2009; Vermeesch et al., 2012; Simons et al., 2012; Eklund, 2010).

Progresses in molecular cytogenetics techniques in the last decade have enabled the interrogation of the AML genomic knowledge. The advent of molecular cytogenetics using comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) microarrays have permitted comprehensive genome-wide assessments at resolutions higher than conventional cytogenetics. Molecular karyotyping enables the elucidation of genetic alterations that may have a significant role in the pathogenesis of AML and could lead to better stratification of diagnosis and prognosis. Chances are that tailored or optimized therapy based on genetic findings could pave the way for improvement in responses to treatment, disease-free survival (DFS) and overall-survival rates (OS).

In contrast to conventional cytogenetics, molecular karyotyping does not depend on mitotically dividing cells, as genomic DNA is used instead of metaphase chromosomes (Heinrichs et al., 2010; Vermeesch et al., 2012; Simons et al., 2012; Heinrichs & Look, 2007). For resolution, molecular karyotyping allows the detection of genomic lesions of ~ 400 kb in size, this surpassing conventional cytogenetics (3-5 Mb) (Wiznieswka et al., 2014) Microarray platforms facilitate customized probes that are designed down to a single exon resolution permitting detection of submicroscopic genetic lesions including microduplications and microdeletions that may be clinically relevant. Moreover, all DNA, tumour and non-tumour is represented and so there is no selection or bias. Besides copy number variations (CNVs), SNP – array facilitates the detection of copy neutral loss of heterozygosity (CN-LOH), also known as uniparental disomy (UPD), otherwise undetectable by conventional cytogenetics (Heinrichs et al., 2010; O'Keefe et al., 2010; Vermeesch et al., 2012; Maciejewski et al., 2009; Heinrichs & Look, 2007).

Therefore, molecular karyotyping using a combination of CGH+SNP DNA microarray can complement conventional cytogenetics not only in the diagnosis but also in the classification and prognostication of AML. In addition, the discovery of cryptic chromosomal aberrations and novel disease related to genomic regions is possible through the utilization of CGH+SNP DNA microarray in a clinical setting.

Objectives of this study

Main Objective

The major objective of this study is to identify somatically-acquired genetic aberrations and their clinical association or significance in AML by using a CGH+SNP DNA microarray platform.

Specific Objectives

This study embarked with the following specific objectives:

I. to detect chromosomal aberrations (CNVs and CN-LOHs) on a genome-wide scale using CGH+SNP DNA microarray in AML
II. to delineate somatic related variants from germline variants in AML
III. to identify recurrent genomic aberrations in AML
IV. to compare the findings from karyotyping and that from CGH+SNP DNA microarray analysis
V. to correlate the prognosis based on karyotyping and molecular genetics with other clinical (age, gender, ethnicity) and laboratory findings (WBC, aberrant antigen expression of CD2, CD4, CD7, CD19 and CD56)

The hypotheses of this study are:

1. CGH+SNP DNA microarray will enable the detection of submicroscopic chromosomal aberrations at a higher resolution as compared to conventional cytogenetics method
2. by comparing tumour versus normal DNA, it would be possible to delineate somatically-acquired genetic aberrations from germline variants in AML
3. CGH+SNP DNA microarray will enable the elucidation of new regions of recurrent genetic aberrations including CNVs and CN-LOHs

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