Research Journal of Biological Sciences 6 (11): 564-568, 2011
ISSN: 1815-8846
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Application of Single Nucleotide Polymorphism (SNP) with the Spatial Indication to Acute Lymphocytic Leukemia (ALL)

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Abstract: In this review, researchers correlate leukemia (ALL) with SNP. The word Acute Lymphocytic Leukemia (ALL) is synonymous with acute lymphoblastic leukemia. The latter term is more commonly used to denote cases in children. Acute leukemia is a rapidly progressing disease that affects frequently cells that are amorphous or immature, i.e., not yet fully developed or differentiated. The relevance of innovative genetic as well as genomic technologies to the study of acute leukemia has commonly be a proving view for such approaches in cancer. Modern day development of high resolution Single-nucleotide Polymorphism (SNP) arrays may possibly comprehensive estimation of the genomes in cancer cell.

Key words: Acute leukemia, Single Nucleotide Polymorphism (SNP), genetic, leukemia, cancer cell, India

INTRODUCTION

A single nucleotide polymorphism is a foundation variation in a genome. A SNP (snip) is a single base mutation in DNA. SNPs are most part simple form and most frequent source of genetic polymorphism. Within the human genome (90% of all human DNA polymorphisms). The text provides an introduction on Single Nucleotide Polymorphisms (SNP) and the inspiration they make presented for current research in ALL genetics and their information. The most significant suggestion following SNP-related research is that genetic deference's linking people in the bearing of predict phenotypes and the study of evolutionary relatedness along with groups of organisms (e.g., species, populations) which is open up through molecular sequencing data and morphological data matrices. Sequence variation caused through SNPs is able to conclude in terms of nucleotide collection, the ratio of the number of base deference's between two genomes over the number of bases compared. This is just about 1/1000 (1/1350) base pairs between two equivalent chromosomes. Near are over 1 million SNPs identified (1,255,326 mapped SNPs at the SNP consortium organization). Confirmation experiments have shown that 95% of these are unique and related polymorphisms (not the product of error or redundancy). Methods for SNP breakthrough and revealing involve a set of biochemical reactions that isolates the exact location of a suspected SNP and then straight-forwardly determines the uniqueness of the SNP by means of an enzyme called DNA polymerase. In addition, many SNPs were initially detected by comparing deferent sequenced genomes. Observe the deference between SNP finding and revealing SNP scoring or SNP genotyping.

Acute Lymphoblastic Leukemia (ALL) is mainly a disease of childhood that arises from recurrent genetic insults that block precursor B and T cell differentiation and drive aberrant cell proliferation and survival. Repeated defects including chromosomal translocations, aneuploidies and gene-specific alterations generate molecular subgroups of B- and T-ALL with differing clinical courses and distinct responses to therapy. Recent discoveries arising from genome-wide surveys and adoptive transfer of leukemia-initiating cells have uncovered multiple gene copy number aberrations and have yielded new insight into at least one type of ALL originating cell.

The understanding of the pathogenesis of ALL has benefited from genetically modified mouse models that go over cellular transformation at specific developmental stages of lymphoid lineage cells. The spectrum of genetic aberrations that promote acute B and T cell leukemias and the mechanisms of cell transformation and malignant

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progression that are reinforced by mouse models of human ALL. Acute leukemias encompass a miscellaneous collection of mainly precursor-stage lymphoid and myeloid cell malignancies. An estimated 18,700+ new cases of acute leukemia are predicted for 2008 (Am. Cancer Soc.) in the United States alone. Almost three-fourths of childhood leukemia (ages 0-19) is Acute Lymphoblastic Leukemia (ALL) whereas Acute Myeloid Leukemia (AML) is the most common form of acute leukemia in adults.

REVIEW OF LITERATURE

Acute Lymphoblastic Leukemia (ALL) results from an acquired genetic injury to the DNA of a single cell in the bone marrow. The disease is often referred to as acute lymphoblastic leukemia because the leukemic cell that replaces the normal marrow is the (leukemic) lymphoblast. ALL is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation. And it results in, the uncontrolled and exaggerated growth and accumulation of cells called lymphoblast or leukemic blasts which fail to function as normal blood cells and the blockade of the production of normal marrow cells leading to a deficiency of red cells (anemia), platelets (thrombocytopenia) and normal white cells (especially neutrophils, i.e., neutropenia) in the blood. ALL occurs most often in the first decade of life but increases in frequency again in older individuals. The cause of ALL is not evident. However, the fundamental finding is that cancers result from genetic malfunction. This happens because there are many check points during the cell cycle which prevent the cell from dividing if there has been some error in replication of DNA or any mutation in the genome. Only when these check points are deregulated cancer results. Further every individual is equally susceptible to cancer. There exists some correlation of the genotype with the predisposition to the cancer. And it is intriguing to work out the density of SNP in order to identify the mischievous nucleotide and the complex diseases.

HISTORICAL BREAKTHROUGH

The discovery of leukemia dates back to the ancient Greeks who recognized this blood disease way back in the 4th or 5th century BC. However, leukemia officially diagnosed for the 1st time by Bennett (1845a) in Edinburgh and was first reported by pathologists Bennett (1845b). Observing an abnormally large number of white blood cells in a blood sample from a patient, Virchow called the condition leukemia meaning white blood. Another pathologist, Franz Ernst Christian Neumann found dirty green-yellow bone marrow (in contrast to the normal red) in a deceased leukemia patient. This finding allowed Neumann to conclude that bone marrow problem was responsible for the abnormal blood of leukemia patients. Leukemia was classified into chronic lymphocytic leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia and acute myelogenous leukemia (erythroleukemia) (Murphy, 1913). The last 2 decades of the 20th century witnessed rapid development of risk-based therapy and the beginnings of bone marrow transplantation as remedy for children with refractory or relapsed leukemia. This could become possible due to tremendous advancement in molecular biology that consequently increased the hopes of all the leukemia patients worldwide.

The development of genome based tools for genetic mapping has opened avenues for sophisticated genetic studies in many eukaryotes and has contributed to rapid increase in the rate of discovery of new genes and gene functions. A host of workers attempted to study the kinematics of chromosomal changes in ALL and to sort out specific alterations that predict treatment outcome. Seeker-walker *et al*. (1978) were the first to present the prognostic importance of leukemic cell chromosomal abnormalities in childhood ALL. On the basis of modal number of chromosomes, they classified ALL into 4 subtypes: hyperdiploid (having >47 chromosomes); pseudodiploid (having 46 chromosomes with structural or numeric abnormalities); diploid (46 chromosomes) and hypodiploid (<46 chromosomes). Translocations are the most common structural chromosomal changes in ALL particularly frequent in the pseudodiploid and hypodiploid groups (Susana, 1993).

In 1980, SNPs were detected using restriction enzyme to identify the presence or absence of cutting sites and scored by observing the resulting fragment length variation. Cooper and Krawczak (1990) classified SNPs according to substitution type (A/C, A/G, A/T, C/G, C/T and G/T). The substitutions were found to occur at a CpG site; a dinucleotide known for its high mutability (Cooper and Youssoufian, 1988). Now there is great interest in developing a third generation genetic map of the human genome composed of SNP markers (Collins *et al*., 1997). Inadequate understanding of leukemogenesis and the neoplastic phenotype of transformed lymphoid progenitors has been a major obstacle to the development of safe, uniformly effective therapy for children with Acute Lymphoblastic Leukemia (ALL).

Studies of isoenzymes, immunologic markers and other expressions of cell phenotype provide valuable clues to ALL etiology but ultimately they fail to divulge mechanisms for leukemic transformation or maintenance

of the malignant state. A more fruitful approach has been used to classify ALL by its cytogenetic features, both numeric and structural (Pui *et al*., 1990). Admittedly, a proportion of the chromosomal changes reported to date have proved to be little more than genetic epiphenomena with vague links to pathogenesis and treatment outcome. This fact not withstanding, the presence of specific cytogenetic abnormalities in leukemic cells has stimulated molecular study of genes near the chromosomal breakpoints and characterization of their protein products (Rowley, 1990). The picture emerging from these investigations is varied but has a consistent theme; genes disrupted by recurrent translocations or other chromosomal alterations tend to participate in cell regulatory pathways that control cell growth and development (Rabbitts, 1991; Green, 1992).

The relative simplicity of SNP genotyping technologies and the abundance of SNPs in human genome made them very popular in recent years. Nickerson *et al.* (1998) and Wang *et al.* (1998) considered SNPs to be the most common form of sequence variation and they expected that highly dense human genetic maps containing >100,000 markers would be developed from the human genome. Dense maps of polymorphic markers are in use in humans (Wang *et al*., 1998; Cargill *et al*., 1999) and there are high hopes that knowledge of an individual's genotype will provide a basis for assessing susceptibility to disease and an optimal choice of therapies (Masood, 1999). A major challenge in realizing these expectations depends on how and when the variants cause disease? Cgry *et al.* (2000) accorded the significance of SNPs as a tool in human cytogenetic. SNPs are distributed throughout the human genome at an estimated overall frequency of at least one in every 1000 base pair (bp) (Carlson *et al*., 2003) but with marked regional differences. SNP arise because of point mutations and are determined by the amount of time since the mutation occurred; evolutionary pressure on biologically significant variants and those linked to the functional variant; random genetic drift and bottleneck events.

Chromosomal imbalances have long been known to be key features of leukaemia. Further, the human genome was found to contain a large amount of genetic variation in the form of sequence polymorphisms. Non-synonymous (ns) SNPs occurring within coding regions are those which produce an amino acid change but are not considered a mutation as a functional protein is still transcribed.

Such nsSNPs are known to affect the functional efficiency of genes (Aplenc and Lange, 2004). For example, drug metabolism and patient response to chemotherapy. SNP's which are found throughout non-coding intronic genome regions are used in major disease linkage and haplotyping studies including the HapMap Project (Altshuler *et al*., 2005) whilst identification of minor regions of amplification or deletion within the genome are facilitated through assessment of SNP copy number (Herr *et al*., 2005). However, genetic variation of the human genome is a promising resource for studying complex diseases such as cancer.

Large number of genetic variations, scattered across the human genome, represent a remarkable opportunity to investigate the etiology, inter-individual deference's in treatment response and outcomes of specific cancer such as leukaemia (Erichsen and Chanock, 2004).

Thus, we are in a position of utilizing such a tool (i.e., SNPs data) to analyze genetic contributions to complex diseases. Such analyses could have big influences on the prevention and early intervention strategies of a disease.

A recent study by Mullighan *et al.* (2007) uses SNP arrays to assess copy number alterations in a large group of childhood and now bioinformatics approaches and resources for single nucleotide polymorphism functional analysis by Mooney (2005). A study by Wang and Scott (2007) to assess leukemia cell DNA obtained from 242 pediatric patients with ALL through the use of SNP arrays, provided the highest resolution analysis of genomic integrity to data. The American Society of Haematology conducted molecular allele-karyotyping of pediatric ALL through high-resolution SNP oligonucleotide genomic microarray (Kawamata *et al*., 2008).

SNP in Mutational Hotspot of WT1 predicts a favorable outcome in patients with cytogenetically normal Acute Myeloid Leukemia (American Society of Clinical Oncology, 2010; Damm *et al*., 2010).

From the foregoing account, it is apparent that ALL is a biologically heterogeneous disorder, therefore. Morphologic, immunologic, cytogenetic, biochemical and molecular genetics depiction of leukemia lymphoblast are needed to establish the diagnosis or to exclude other possible causes of bone marrow failure and finally to classify ALL subtypes. However, only a few genetic markers are known to have significant prognostic implications in ALL patients.

CONCLUSION

In the present time, researchers creating innovative approaches that would avoid leukaemia and their correlate

genetics diseases. With the intention of so many researcher paved the way for SNP identification and their genetically analysis, this advances technology for understanding of the genetics of acute lymphoblastic leukaemia. Now-a-day's emerging molecular technologies suggest that genetic defects of leukaemic cells could revolutionize management of this disease. There are number of bioinformatics tools as well as online server for SNP analysis predicts function and structural annotation. These program users friendly and give much aware results.

ACKNOWLEDGEMENT

The researchers thank Prof. Dr. Usha Nair, Department of Chemistry Government, M.V.M. College Bhopal for her kind support.

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