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# Clusters of CDK2, CCND1, and CMYC genes involved in cancers: Acute Lymphocytic Leukemia (ALL) as a model

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**Abstract**
Cancer is not a single disease but it involves changes in multifunctional genes, the causes for these changes remain less understood. It is now becoming clear that multiple genes orchestrate to turn on the carcinogenesis process. These genes involve several signaling pathways which then characterize uncontrolled cell divisions. Our aim was to study cell cycle genes CDK2, CCND1, and c-MYC to determine their clustering in the evolutionary pathway and to understand their diversions leading to continued cell division processes. Since Acute Lymphoblastic Leukemia (ALL) is the most prevalent form of cancer in children we took this as a model for analyzing the role of these genes in the leukemia process. The prevalence/spread of these genes was found to be very limited in the animal kingdom; hence the question is whether this may be due to the fact that during evolution in time there could have been loss of some functions or mutations in these genes which relates to the switch function of these genes. Alternatively, have they evolved in a way which we are unable to trace due to limited methodology? Further, with the results analyzed so far we can imagine that these species in which we found the presence of these genes across the animal kingdom could have had cancer like diseases during their lifetime. We conclude that each of these genes formed several clusters which were typical of their role/functions in ALL.

**Keywords:** ALL; Cell cycle genes; Gene clusters; Phylogeny; CDK2; CCND1; c-Myc.

## Introduction

Acute Lymphoblastic Leukemia (ALL) is one of the most frequent types of cancer that afflicts children. It is characterized by accumulation of immature lymphocyte progenitor cells in the bone marrow. Although current long term survival rate in children is above 80%, this disease is not completely curable with the available treatment strategies (Crazzolara and Bendall 2009). A better understanding of the underlying mechanisms behind ALL requires information about the changes that occur during cell cycle and the genes that are involved in the process. Our earlier studies on leukemia in children determined the role of susceptibility biomarkers and risk factors (Reddy *et al.* 2006; Reddy and Jamil 2006; Jamil and Reddy 2007), further we also determined the SNP changes in drug metabolizing genes like GSTs and FLT3 which relate to drug–gene interactions (Reddy *et al.* 2006, Kumar *et al.* 2011), the signaling pathways and biomarkers of hematological malignancies were also determined (Mani *et al.* 2006, 2007). Cell division in organisms is regulated by a family of cyclin dependent kinases (CDKs), which consist of a subunit of CDK and an activating cyclin subunit. These CDK complexes phosphorylate several substrates such as the Retinoblastoma family of proteins, which are negative regulators of cell cycle. The inactivation of these CDKs is also part of the typical cell cycle process. The inhibitors of CDK such as p16Ink4a, p15Ink4b, p27Kip1, and p21Cip1 negatively regulate CDK activities (D'Andrilli *et al.* 2004). The cell cycle process is regulated by the tumor suppressor gene, p53. Several other genes and proteins are also involved in the normal cell cycle process.

Several studies have been carried out to determine the changes in the cell cycle that lead to leukemogenesis. Homozygous inactivation of p16 INK4 gene has been reported in childhood ALL by several researchers (Okuda *et al.* 1995; Lemos *et al.* 2003). Aberrant p15 promoter methylation (Batova *et al.* 1997) and deletion of p15 (Okuda *et al.* 1995) have been reported in several cases of childhood ALL. A study based on a population of Chinese children has implicated polymorphism of cyclin D1 (CCND1) in relation to occurrence of ALL (Hou *et al.* 2005). Several studies have reported deletion of p27/Kip1 gene in childhood ALL (Markaki *et al.* 2006; Takeuchi *et al.* 2006). CDK2 catalytic activity was reported in a sample of childhood

ALL samples using in vitro kinase assays (Schmitz *et al.* 2005). Studies on Notch-1 regulatory mechanisms have suggested that c-Myc deregulation may be part of the early events in T-cell leukemogenesis (Palomero *et al.* 2006; Weng *et al.* 2006). Overexpression of MDM2 has been reported in 15–25% of ALL patients at the time of diagnosis (Hendy *et al.* 2009). Tumor suppressor gene, Tp53, mutations have been reported in some children with ALL, though it is more frequently associated with relapse patients (Kawamura *et al.* 1995).

In the present study, sequences of selected genes involved in the cell cycle pathway were selected to infer phylogeny as well as to determine their homology across various species in the animal kingdom to better understand how these genes contribute to leukemogenesis**.** Although the same cell cycle genes exist in various organisms across the animal kingdom, but they function differently in different organisms, while in humans when these genes develop mutations leukemogenesis occurs. A study of this nature might help in better understanding leukemogenic pathway in humans.

## Materials and Methods

*(a) Search for cell cycle genes in ALL*

Literature databases were queried to devise a list of genes which are involved in cell cycle and have been reported in association with ALL (Table 1). Further information about each of the genes in the list was obtained by querying GeneCards database version 3 (Safran *et al.* 2010) (www.genecards.org).

*(b) DNA sequence data and sequence alignment*

Three genes were selected for the study from the list of cell cycle genes. NCBI GenBank database (Benson *et al.* 2011) (at www.ncbi.nlm.nih.gov/) was queried to retrieve all available nucleotide sequences, across various species, of the mRNA transcript of the genes. These sequences were saved as fasta file and were used for further analysis. The sequences were first imported into the alignment explorer of MEGA version 4 software (Tamura *et al.* 2007). An initial multiple sequence alignment was carried out using the Clustal W (Thompson *et al.* 1994) algorithm. The aligned sequences were further manually edited and again aligned using Clustal W with default parameters for Gap Opening, Gap Extension Penalty and DNA weight matrix to obtain optimal global sequence alignment. This multiple sequence alignment file was then used to infer phylogeny.

*(c) Phylogenetic tree construction*

Phylogeny was reconstructed using MEGA version 4.0. The distance based Neighbour-Joining (Saitou and Nei 1987) method was chosen for phylogeny reconstruction of the sequences. Kimura 2-parameter (Kimura 1980) distance model, which assumes uniform rate of substitution among sites, was selected as the nucleotide substitution model. To further increase the reliability of the phylogenetic tree obtained, 1000 Bootstrap replications were performed.

*(d) Functional divergence*

Functional divergence is useful in identifying sites/residues that are subjected to functional constraints during evolution. In this study, functional divergence between the various species for each gene was calculated using Diverge 1.04 software (Gu and Velden 1999). Sequences of the corresponding proteins encoded by the genes were aligned using Clustal W in MEGA software using default parameters and this alignment was used as input for the software. Using this input, the software was used to build a Kimura 2 parameter tree to delineate clusters. These clusters were then used to estimate statistical parameters such as site specific profile, which is useful to predict the amino acid residues which are vital for functional divergence. Residues estimated to have a functional divergence value greater than 0.1 were highlighted in the sequence alignment.

## Results

*(i) Phylogenetic analysis*

From the genes listed in Table 1 we selected three genes CDK2 (606 bp), CCND1 (526 bp) and c-MYC (509 bp) genes and determined their phylogeny after multiple sequence alignment.

**Table 1: Cell cycle genes associated with Acute Lymphoblastic Leukemia.**

| S.No. | Gene Name | Function | Reference | GeneCards ID |
|---|---|---|---|---|
| 1 | p53 | regulates target genes that induce cell cycle arrest | Wojcik *et al.* 2005 | GC17M007565 |
| 2 | p16INK4A (CDKN2A) | Capable of inducing cell cycle arrest in G1 and G2 phases. | Lemos *et al.* 2003 | GC09M021957 |
| 3 | p15 (CDKN2B) | Encodes a protein that functions as a cell growth regulator that controls cell cycle G1 progression | Iravani *et al.* 1997 | GC09M021992 |
| 4 | Cyclin D1 (CCND1) | Essential for the control of the cell cycle at the G1/S (start) transition | Hou *et al.* 2005; Aref *et al.* 2006 | GC11P069455 |
| 5 | c-MYB | play a critical role in regulating the G(1)/S cell cycle transition | Clappier *et al.* 2007 | GC06P135544 |
| 6 | CDK2 | involved in the control of the cell cycle | Schmitz *et al.* 2005 | GC12P056360 |
| 7 | CDKN1B (p27, Kip1) | Important regulator of cell cycle progression | Markaki *et al.* 2006 | GC12P012768 |
| 8 | CDK6 | Probably involved in the control of the cell cycle | Chilosi *et al.* 1998 | GC07M092234 |
| 9 | CDKN1A (p21, Cip1) | functions as a regulator of cell cycle progression at G1 | Roman-Gomez *et al.* 2002 | GC06P036645 |
| 10 | CCND2 | Essential for the control of the cell cycle at the G1/S (start) transition | Clappier *et al.* 2006 | GC12P004382 |
| 11 | ABL1 | Regulates cytoskeleton remodeling during cell differentiation, cell division and cell adhesion. | Chiaretti *et al.* 2007 | GC09P133589 |
| 12 | CCND3 | Essential for the control of the cell cycle at the G1/S (start) transition. | Sicinska *et al.* 2003 | GC06M041949 |
| 13 | CDKN1C (p57, Kip2) | Negative regulator of cell proliferation. May play a role in maintenance of the non-proliferative state throughout life | Gutiérrez *et al.* 2005 | GC11M002861 |
| 14 | c-MYC | plays a role in cell cycle progression, apoptosis and cellular transformation | Weng *et al.* 2006 | GC08P128748 |
| 15 | Rb1 | key regulator of entry into cell division that acts as a tumor suppressor | Schmitz *et al.* 2005; Tsai *et al.* 1996 | GC13P048877 |
| 16 | MDM2 | affects the cell cycle, apoptosis, and tumorigenesis through interactions with other proteins | Hendy *et al.* 2009; Zhou *et al.* 2003 | GC12P069201 |
| 17 | ATM | important cell cycle checkpoint kinase | Gumy *et al.* 2003 | GC11P108127 |

**CDK2**

From Genbank database we obtained sequences of seventeen species, which were used in the construction of phylogenetic unrooted tree for CDK2 (Figure 1), which could be grouped in five clusters, one cluster with humans and other Mammals, an isolated cluster of Red Jungle Fowl, one cluster with different species of Fish, a cluster of Amphibians, a final cluster consisting of other organisms. Information about the gene was obtained from GeneCards database (GCid: GC12P056360).

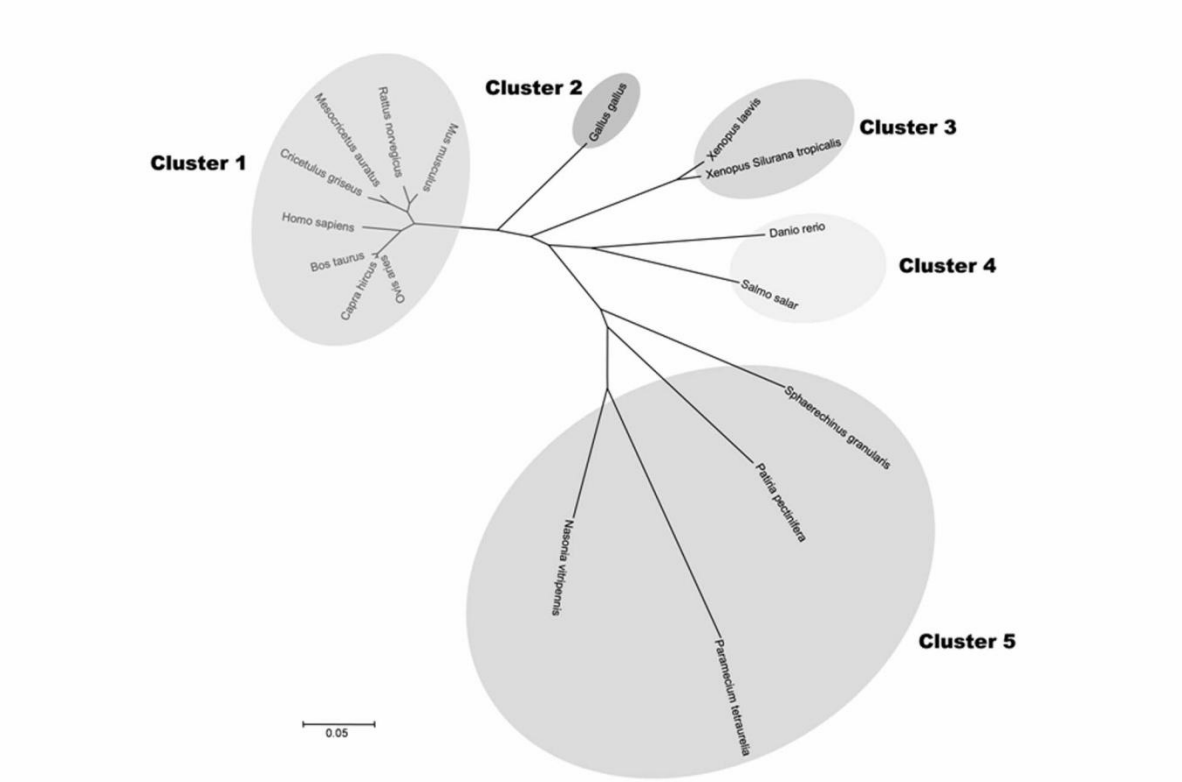



**Figure 1: Phylogenetic tree of CDK2.**

**Table 2: Sequence details of CDK2.**

| S.No. | Organism | Common Name | Accession Number (Nucleotide) | Accession Number (Protein) |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | *Homo sapiens* | Human | X62071 | CAA43985 |
| 2 | *Bostaurus* | Cattle | BT020790 | AAX08807 |
| 3 | *Cricetulusgriseus* | Chinese Hamster | AJ223949 | CAA11680 |
| 4 | *Rattusnorvegicus* | Norway Rat | NM_199501 | NP_955795 |
| 5 | *Musmusculus* | House Mouse | NM_183417 | NP_904326 |
| 6 | *Ovisaries* | Sheep | NM_001142509 | NP_001135981 |
| 7 | *Mesocricetusauratus* | Golden Hamster | D17350 | BAA04165 |
| 8 | *Capra hircus* | Goat | EF035041 | ABK34941 |
| **Cluster 2** | | | | |
| 9 | *Gallus gallus* | Red Jungle Fowl | NM_001199857 | NP_001186786 |
| **Cluster 3** | | | | |
| 10 | *Xenopuslaevis* | African Clawed Frog | NM_001090651 | NP_001084120 |
| 11 | *Xenopus (Silurana) tropicalis* | Western Clawed Frog | NM_001008135 | NP_001008136 |
| **Cluster 4** | | | | |
| 12 | *Daniorerio* | Zebrafish | NM_213406 | NP_998571 |
| 13 | *Salmosalar* | Atlantic Salmon | NM_001141734 | NP_001135206 |
| **Cluster 5** | | | | |
| 14 | *Sphaerechinusgranularis* | Purple Sea Urchin | AJ224917 | CAA12223 |
| 15 | *Patiriapectinifera* | Starfish | AB481376 | BAH97197 |
| 16 | *Nasoniavitripennis* | Jewel Wasp | NM_001161462 | NP_001154934 |
| 17 | *Paramecium tetraurelia* | Paramecium | AF126147 | AAD34354 |

**CCND1**

Analyzing the phylogenetic tree constructed using sequences of cyclin D1 from thirteen species revealed four clusters – a cluster consisting of humans and few other Mammals, an isolated cluster of Red Jungle Fowl, a cluster with two species of Amphibians and a cluster of Fish (Figure 2). Information about the gene was accessed from GeneCards database by querying with GCid: GC11P069455.

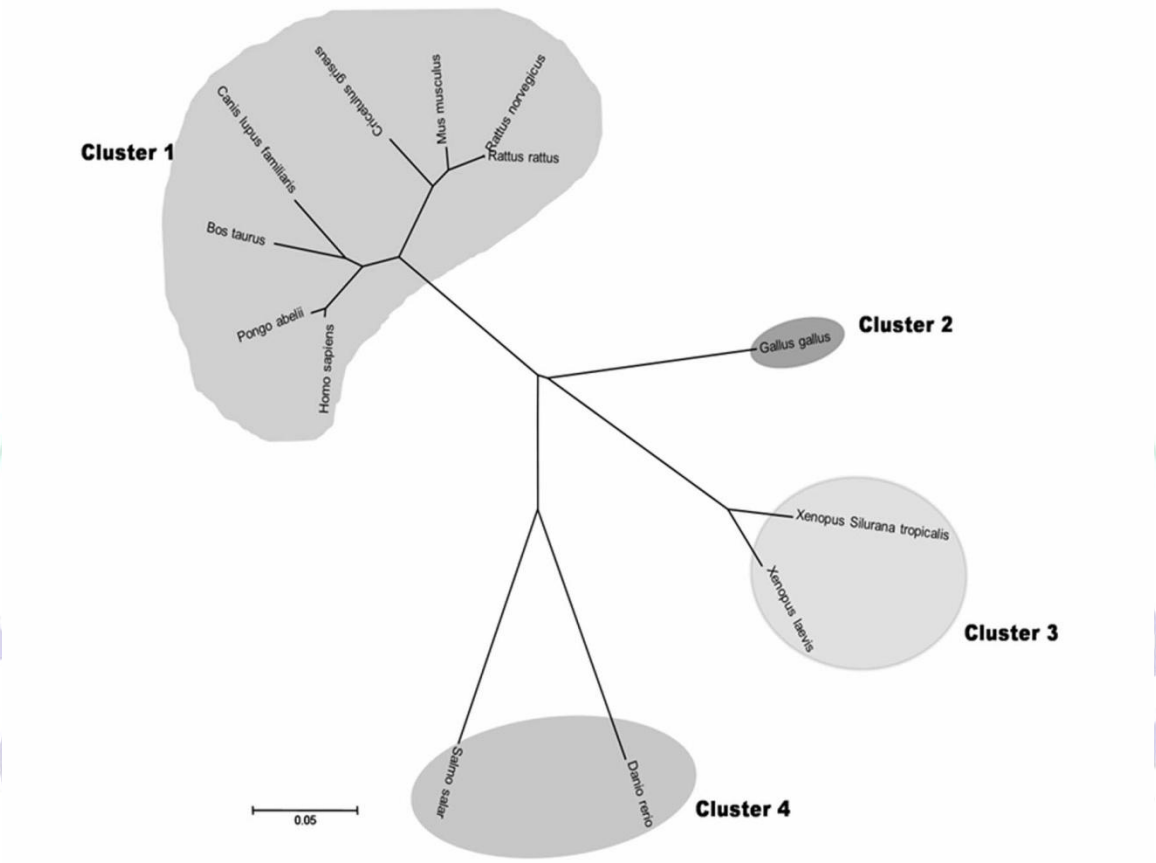



**Figure 2: Phylogenetic tree of CCND1.**

**Table 3: Sequence details of CCND1.**

| S.No. | Organism | Common Name | Accession Number (Nucleotide) | Accession Number (Protein) |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | *Homo sapiens* | Human | NM_053056 | NP_444284 |
| 2 | *Musmusculus* | House Mouse | S78355 | AAB34495 |
| 3 | *Rattusnorvegicus* | Norway Rat | X75207 | CAA53020 |
| 4 | *Cricetulusgriseus* | Chinese Hamster | EF524275 | ABP73256 |
| 5 | *Pongoabelii* | Sumatran Orangutan | NM_001131301 | NP_001124773 |
| 6 | *Bostaurus* | Cattle | BC112798 | AAI12799 |
| 7 | *Rattusrattus* | Black Rat | D14014 | BAA03115 |
| 8 | *Canis lupus familiaris* | Dog | NM_001005757 | NP_001005757 |
| **Cluster 2** | | | | |
| 9 | *Gallus gallus* | Red Jungle Fowl | U40844 | AAA83271 |
| **Cluster 3** | | | | |
| 10 | *Xenopuslaevis* | African Clawed Frog | X89475 | CAA61664 |
| 11 | *Xenopus (Silurana) tropicalis* | Western Clawed Frog | NM_001005452 | NP_001005452 |
| **Cluster 4** | | | | |
| 12 | *Daniorerio* | Zebrafish | AF365874 | AAM00355 |
| 13 | *Salmosalar* | Atlantic Salmon | NM_001165391 | NP_001158863 |

**c-MYC**

Sequences from seventeen species were used to infer phylogeny resulting in five clusters, a cluster of ten Mammalian species, a single isolated cluster of Red Jungle Fowl, a single cluster of Amphibians, a cluster consisting of Fish and a cluster with a species of hemichordate and Atlantic salmon (Figure 3). Information about the gene was accessed from GeneCards database (GCid: GC08P128748).

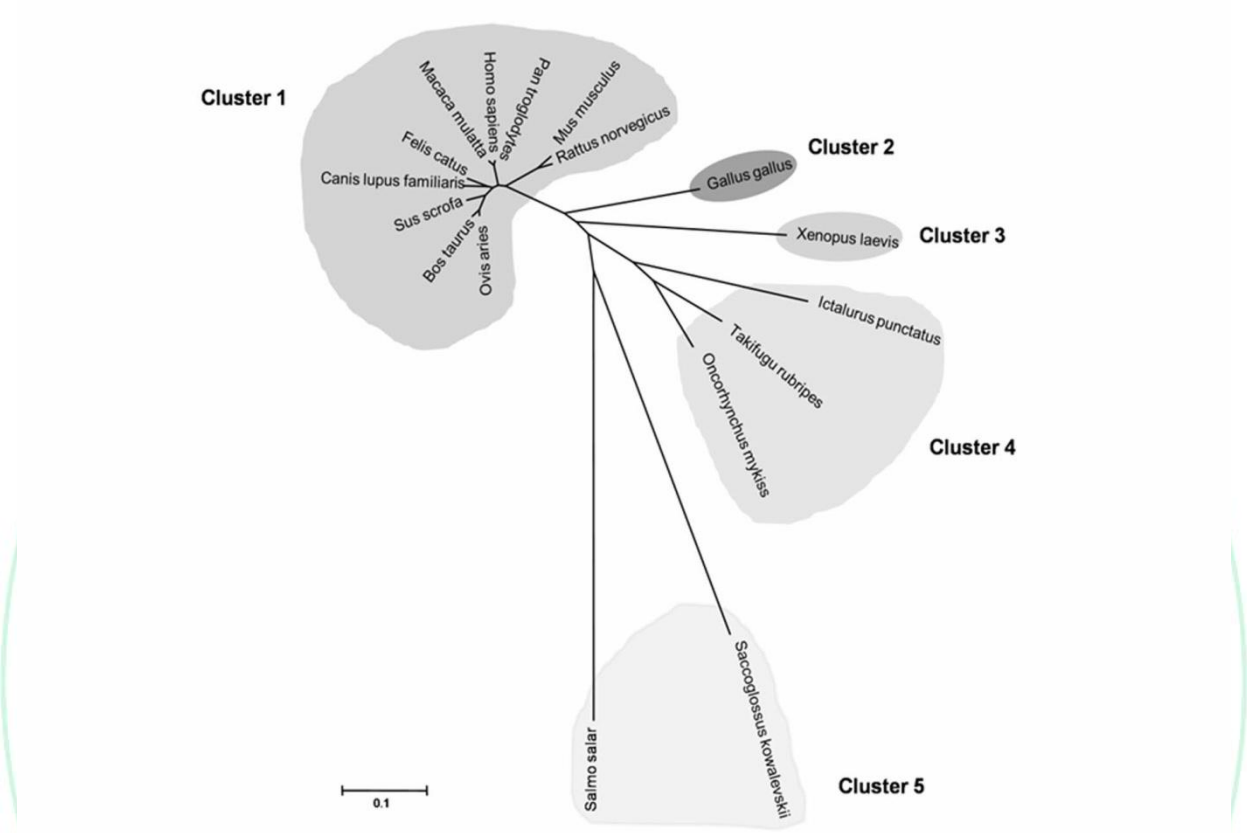



**Figure 3: Phylogenetic tree of cMYC.**

*(ii) Functional divergence*

We used Diverge 1.04 to calculate the functional divergence of CDK2, CCND1 and c-MYC genes. In our analysis, CDK2 and CCND1 genes showed no significant functional divergence. This result could probably indicate that these two genes are highly conserved, especially in Mammalian species.For the functional divergence analysis, the c-MYC gene was designated into two clusters-the first cluster is composed of species other than Mammals and the second cluster contained all the Mammalian species. The coefficient of functional divergence between these two clusters was 0.41. We found 317 residues to have a posterior probability greater than 0.1.These residues showed a higher degree of variability in species belonging to cluster one than cluster two (Figure 4).

**Discussion**

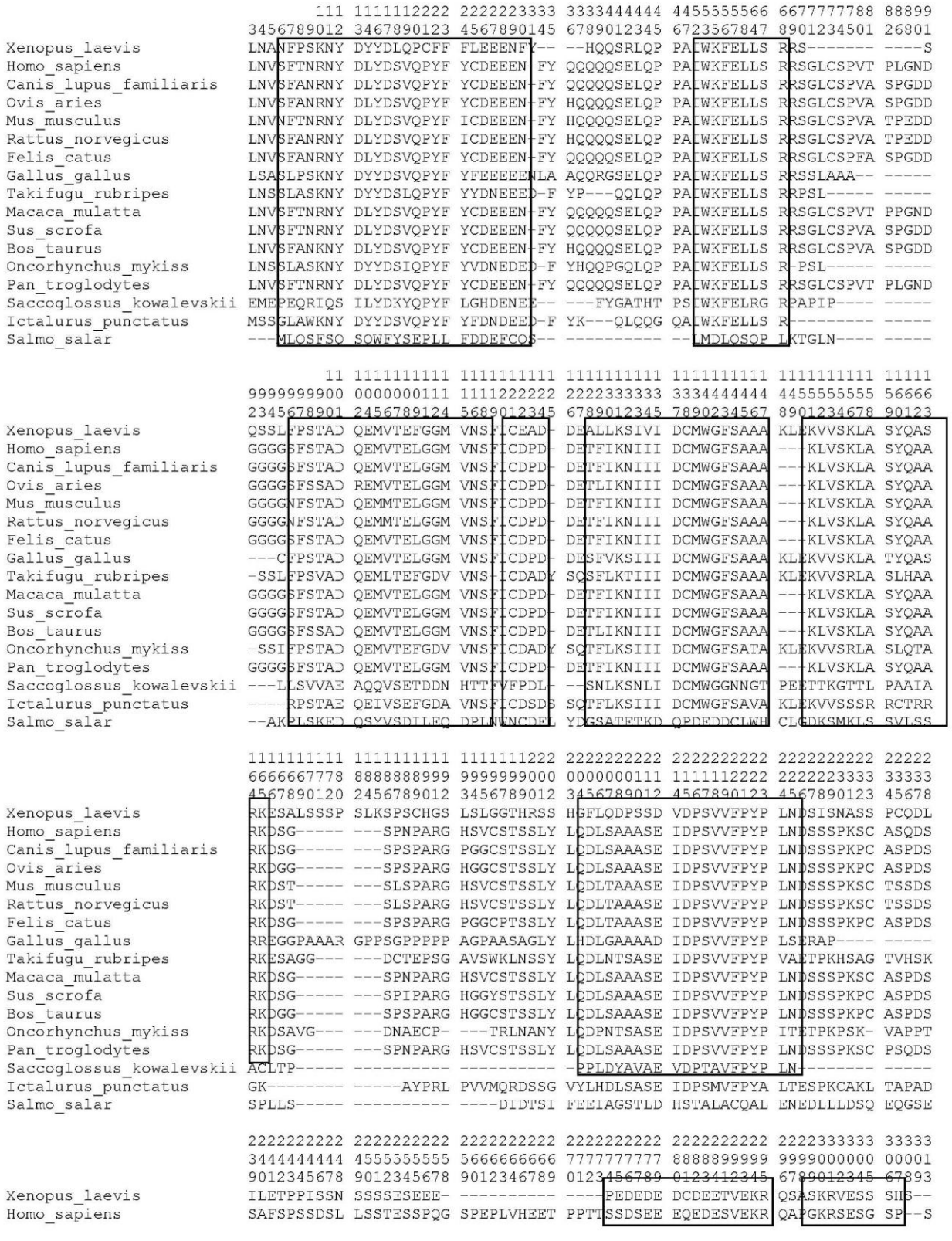
Loss of cell cycle regulation through changes in cell cycle gene in the bone marrow is a common cause for the progress of tumorigenesis process. ALL is a serious pediatric malignancy, exhibiting both normal and proliferative controls and blocking differentiation into functional cells. In ALL mostly cells reside in the G-1 phase, and only a few cells proceed to the next G0 phase. In normal cells during cell cycle progression early G1 cells respond to environmental stimuli inducing differentiation. However, in disease condition the cells do not respond or do not recognize the signals and no longer respond to differentiation process. It has been reported that cyclin dependent kinase CDK2 was active in ALL and contributed to the disease condition. The catalytic activity of CDK2 was reported to increase in childhood leukemia (Schmitz *et al.*

2005). Further it was suggested by these authors that CDK2 contributed to the functional inactivation of Retinoblastoma gene (Rb). In view of the above findings it was important to determine the role of CDK2.

**Table 4: Sequence details of cMYC.**

| S.No. | Organism | Common Name | Accession Number(Nucleotide) | Accession Number (Protein) |
|---|---|---|---|---|
| **Cluster 1** | | | | |
| 1 | *Homo sapiens* | Human | V00568 | CAA23831 |
| 2 | *Canis lupus familiaris* | Dog | X95367 | CAA64654 |
| 3 | *Ovisaries* | Sheep | Z68501 | CAA92814 |
| 4 | *Musmusculus* | House Mouse | NM_010849 | NP_034979 |
| 5 | *Rattusnorvegicus* | Norway Rat | NM_012603 | NP_036735 |
| 6 | *Feliscatus* | Domestic Cat | NM_001173446 | NP_001166917 |
| 7 | *Susscrofa* | Pig | FJ882404 | ACQ76904 |
| 8 | *Macacamulatta* | Rhesus Monkey | NM_001142873 | NP_001136345 |
| 9 | *Bostaurus* | Cattle | NM_001046074 | NP_001039539 |
| 10 | *Pan troglodytes* | Chimpanzee | NM_001142794 | NP_001136266 |
| **Cluster 2** | | | | |
| 11 | *Gallus gallus* | Red Jungle Fowl | NM_001030952 | NP_001026123 |
| **Cluster 3** | | | | |
| 12 | *Xenopuslaevis* | African Clawed Frog | X14806 | CAA32911 |
| **Cluster 4** | | | | |
| 13 | *Takifugurubripes* | Tiger Puffer | AB236413 | BAE45315 |
| 14 | *Oncorhynchusmykiss* | Rainbow Trout | AJ627208 | CAF25507 |
| 15 | *Ictaluruspunctatus* | Channel Catfish | AF283994 | AF283994 |
| **Cluster 5** | | | | |
| 16 | *Saccoglossuskowalevskii* | Acorn Worm | NM_001164972 | NP_001158444 |
| 17 | *Salmosalar* | Atlantic Salmon | NM_001173816 | NP_001167287 |

Cyclin D1 is an important cell cycle regulatory protein, which is involved in the transition of cell cycle from G1 phase to S phase during the process of cell division. Change in cell cycle kinetics and acceleration of G1 phase, which might lead to abnormal cell proliferation, has been associated with overexpression of this protein (Pabalan *et al.* 2008). During early G1 phase, Cyclin D1 binds to and activates CDK4 and CDK6 kinases, which leads to phosphorylation of Retinoblastoma protein, thus contributing to its inactivation. Studies have reported overexpression of cyclin D1 in patients with ALL and have suggested that cyclin D1 may play a role in mobilization of blast cell from the Bone Marrow to lymph nodes (Aref *et al.* 2006). These reports indicate that CCND1 could serve as a prognostic marker in the detection of ALL and hence needs to be investigated in more detail to elicit information regarding its role in tumorigenesis. The c-Myc proto-oncogene encodes a transcription factor that is essential for cell growth and proliferation. It has also been reported in the control of DNA replication. It dimerizes with a protein called Max, to bind Enhancer Box sequences (E-boxes) and recruits histone acetyltransferases for regulation of gene expression. The c-Myc proto-oncogene is involved in transformation and cell proliferation partly through activation of cyclin D2 promoter and also induces programmed cell death which is mediated by nuclear respiratory factor 1 (NRF-1) and the Arf-p53 pathway (Luo *et al.*. 2005). In normal cells, c-MYC regulation is induced and regulated by mitogenic stimulation. In the absence of this induction, the cells revert back to the non-proliferative state. Studies suggest that in cancer cells, there is an absence of stringency in regulation attributed to mutations in the regulation of Myc genes and the persistent induction of Myc expression through oncogenic signals that lie upstream such as Wnt/β-catenin, Notch or RTK/Ras pathways (Sodir and Evan 2009). Translocations t(8;14), t(8;22), and t(2;8) involving *MYC* deregulation have been reported in 2%-5% of childhood ALL along with reports of aberrant c-Myc stability in cell lines and bone marrow samples in pediatric patients. Studies have reported that *MYC* is a direct transcriptional target of oncogenic Notch1, which is common in T-ALL. These studies indicate the need to delve further into the exact correlation





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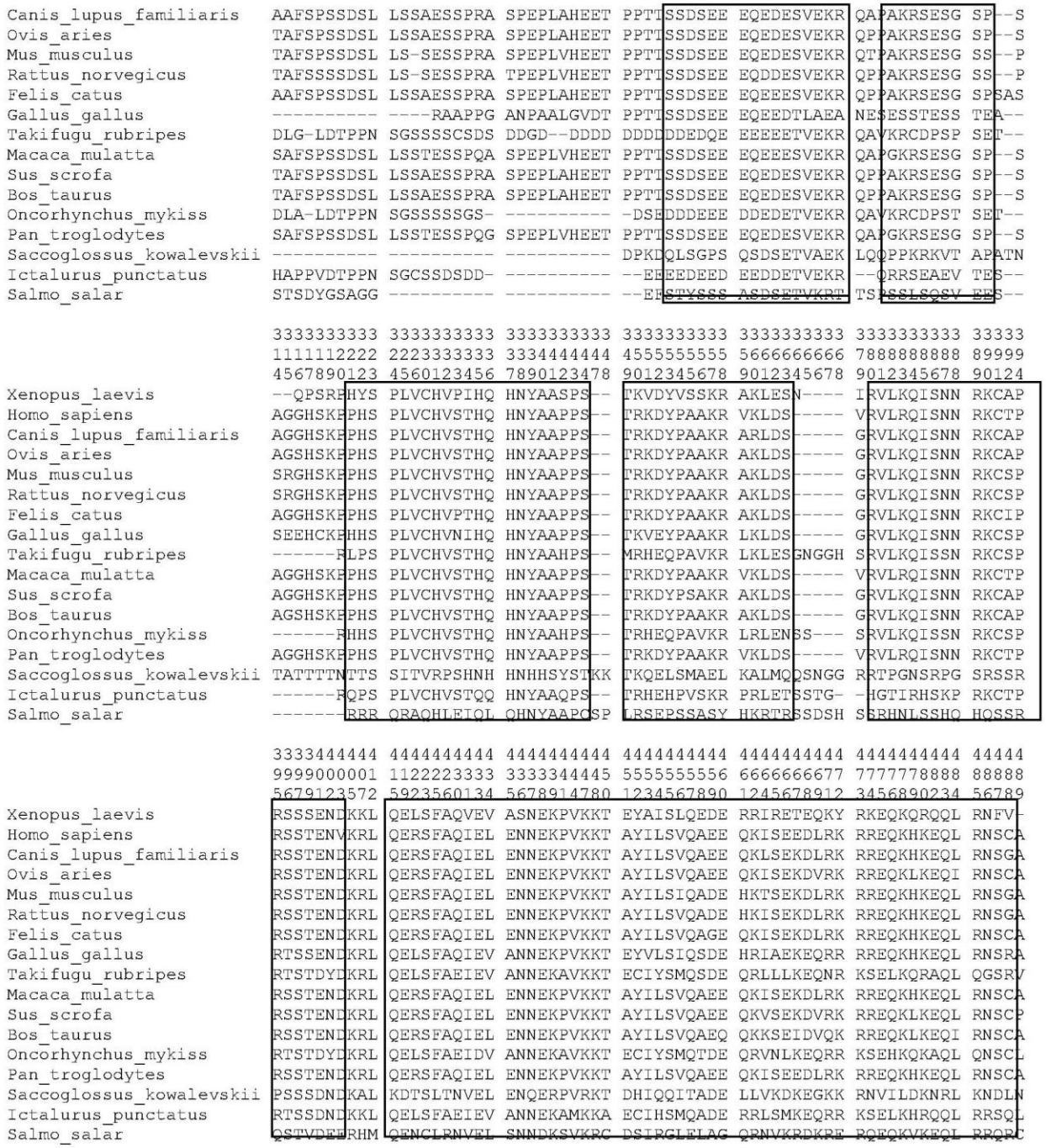


**Figure 4: Significantly divergent residues highlighted in c-MYC sequence alignment.**

between c-MYC and leukemogenesis (Delgado and León 2010).

Phylogenetic studies play an essential role in understanding evolutionary history of genes and their impact on disease etiology. Several studies have calculated the functional divergence of genes based on phylogenetic reconstruction across various species and

further implicate those sites which are subjected to functional constraints during evolution (Khan and Jamil 2008; Khan and Jamil 2010). Further, this information could be used to observe drug-gene interactions with the help of homology modeling and affinity modeling studies (Kotra *et al.* 2008). Our earlier studies on phylogeny of p53 and MDM2 revealed that these genes show a high degree of sequence similarity in Mammals, suggesting parallel carcinogenesis pathways involving these genes in the Mammalian species (Jayaraman *et al.* 2011).

Studies based on evidence from paleontology and genetics suggest that mechanisms of cancer are embedded deeply throughout evolution. Understanding the phylogenetic evolution of these genes could help in furthering our knowledge on the mechanisms involved in cancer (Davies and Lineweaver 2011).

In the present study, we applied bioinformatics approaches to mine databases to garner information regarding the CDK2, CCND1 and c-MYC cell cycle genes and their role in ALL. We inferred phylogeny of these genes across various species, for which sequence information is available in the databases. Analysis of the sequence alignments indicates that throughout the mammalian species, these genes are mostly similar/exhibit sequence homology and thus group under a single cluster. Though the avian species, the amphibians and the some species of fish tend to form three separate clusters due to the variation in their sequences, there appears to be a moderate degree of sequence similarity with those of mammalian species.

In our study of the phylogenetic analysis and tree constructed using sequences of these three genes, we observed that these gene sequences are more or less similar across these few taxa, this might indicate the presence of cancer like disease genes in the evolutionary history of these species.

In the future, when the sequence information for these genes across a wide range of taxa becomes available, a more intensive phylogenetic analysis would be possible which could help in delving further into the changes and the mechanisms of change through which these genes contribute to the evolution of leukemogenesis process and also assist in designing effective therapeutic measures.

*Correlation between CDK2, CCND1, c-MYC*

CDK2, cyclin D1 and c-MYC genes are important components in the cell cycle pathway. Alterations in these genes have been reported in association with malignant transformations. Studies have reported that c-MYC gene might be involved stimulating the activity of cyclin E/CDK2 complex. The phosphorylation of MYC by CDK2 is helpful in suppression of senescence (Hydbring and Larsson 2010). c-MYC gene has also been reported to regulate the expression of cyclin D1 at an early stage of the cell cycle process. Cyclin D1–CDK2 complex might indirectly promote cell proliferation by sequestering p21 and p27 genes this complex has been detected previously in breast cancer cell lines and was reported to exhibit several features of transformation (Chytil *et al.* 2004). These studies indicated that the three genes functionally interact with each other and play a role in direct/indirect regulation of the other genes. It is essential to better understand the association between these genes because their interaction might be a significant aspect in the tumorigenesis process.

**Conflict of Interests**

Authors have no conflicting interests.

**Acknowledgement**

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