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REVIEW ARTICLE

Can Genomic Variations in Acute Lymphoblastic Leukemia Direct Prognosis and Treatment?

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ABSTRACT: Acute Lymphoblastic Leukemia (ALL) is the most common form of leukemia in children. ALL occurs when the body produces an extreme number of lymphocytes. The International Consensus Classification (ICC) separates ALL into two separate subcategories, T Acute Lymphoblastic Leukemia (T-ALL) and B Acute Lymphoblastic Leukemia (B-ALL). While some patients are able to be cured, for other patients many common treatments do not work and often this failure results in the death of the patient. This review investigates genetic mutations to determine whether genetic variations in ALL can direct prognosis and treatment. This article aims to build on prior work by discussing specific mutations and providing a broader perspective of the topic as well, and emphasizes areas of potential impact for future research. After carefully reviewing genetic mutations commonly found in ALL patients, nine distinct categories were identified which impact the prognosis or treatment of the disease. Some mutation types impacted patient survival rates drastically, while others rendered certain treatments essentially useless. These results are important because by examining genetic rearrangements in ALL in greater depth and using them to direct patient care, countless children and adults will benefit from more effective treatments provided by more knowledgeable clinicians.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Acute Lymphoblastic Leukemia; B-Cell ALL; T-Cell ALL.

Introduction

Leukemia is a type of cancer which originates in the bone marrow. This is the soft and spongy tissue which is present within most bones in the human body. The bone marrow sometimes works irregularly and begins to develop abnormal blood cells which grow normally and keep evolving, but peak at one point before becoming a proper blood cell.[1] They continue taking nutrients from other cells, duplicating and expanding to other parts of the body. There are four types of Leukemia: Acute Lymphocytic Leukemia (ALL), Acute Myelogenous Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), and Chronic Myelogenous Leukemia (CML). This article focuses on Acute Lymphocytic Leukemia. Of all the four forms of leukemia, ALL stands to be the most common type, especially in children. The difference between this type and others is that it originates in the lymphoid cells of the bone marrow and spreads rapidly into the blood.[2] ALL can be defined and differentiated by various cytogenetic variations. Recent progress in molecular techniques, specifically next generation sequencing, has allowed researchers to study variants and develop a more thorough understanding.

This paper plans to demonstrate how examining the different genetic variations in each ALL patient specifically will be able to direct prognosis and treatment more accurately and more efficiently. This paper will illustrate gene variations and chromosomal abnormalities, providing an overview for background knowledge before going into depth about prognosis and treatment. The approach used is to examine case studies and articles which already exist and review parts of them to arrive at a holistic conclusion.

ALL has different percentage chances of affecting persons depending on factors like age and race. Persons under the age of five are most likely to be diagnosed with ALL.[3] Ages five to 25 have the most minimal risk, but the chances increase slightly at ages 25-50. 60% of ALL cases are in children. Figure 1 illustrates how risk levels tend to lower as the age groups get older, showing that this is more of a pediatric cancer despite being present in both adult and child patients. Many factors such as the way children can handle more aggressive therapy in a better way than adults, result in the conclusion that children have a much better prognosis than adults in ALL cases.[3]

ALL has various symptoms and signs that can be detected. If one experiences anything listed here, they are at particular risk for ALL because these are recurrent symptoms in ALL patients. These symptoms include unexplained tiredness and weakness; feeling extremely hot temperatures at night compared to room temperature; fevers and sweating; being more prone to bruises and scabs; little pinpoint spots under the skin known as Petechiae; or having trouble breathing. Pain in the bones, stomach, or below the ribs is also included on this list. Little lumps in the groin, underarms, stomach, or neck, which don't give pain, are also common. Finally, having an abnormally large number of separate infections can also be a symptom.[4]

Therapeutic methods for treating ALL can be extremely costly in America. For adolescents, young adults, and children, the overall cost for ALL treatment increased to the average of around $612,779. Professional services and hospital visits make up 42.5% of that overall cost.[5] By studying genetic variations specifically, doctors can tailor treatments better to individuals and potentially lower that cost.

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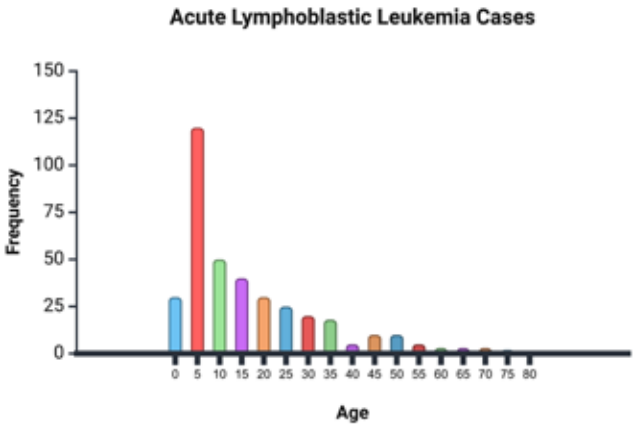

Figure 1: Image adapted from PubMed Article.[6] Describes the general frequency of ALL cases by various age groups.

Importance:

There are various gene variations which are repeatedly discovered and noticed within patients with ALL. These genetic variations have large impacts and can greatly affect the course of the disease and the patient's reactions to various treatment methods.

Genes are extremely complex and thus are bound to have abnormalities person by person. Many of these abnormalities are repeatedly found. Some of these abnormalities are associated with ALL and consistently found in various patients. This section will review many available known variations, including chromosomal variations and variations between different genes. Chromosomal variations are changes in the structure or number of chromosomes that can lead to genetic disorders and variations between different genes, including deletions, translocations, inclusions, and repressors. For example, 60- 80% of patients with ALL have abnormalities in chromosome number or structural rearrangements (translocations), whereas the remaining 20-40% have normal karyotypes.[7]

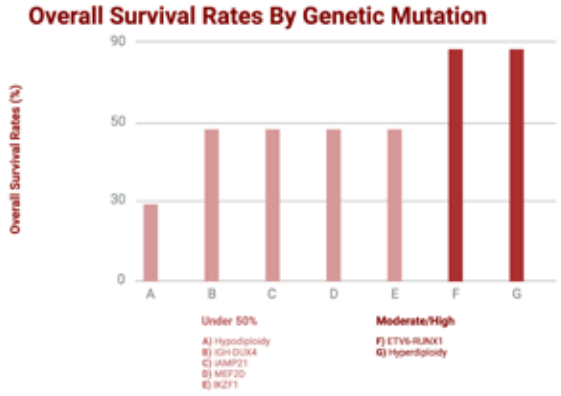

Figure 2: Chart describing the differences in survival rates dependent on genetic mutations present within the patient. Darker colors symbolizing OS percentages higher than 50%, with lighter colors symbolizing mutations with OS rates under 50%.

When one gets diagnosed with a disease, the future is the first thing discussed virtually one hundred percent of the time. Questions such as whether they will live, how long the process will take, whether they will ever be completely cured are always asked or in the patient's mind. Doctors commonly address these concerns using previous patients who went through similar or the same situations. The problem with this is that, while two patients living similar lifestyles with similar exercise and eating habits might have the same exact subcategory of the same disease, they might still have differences in how the disease affects their bodies in the future. As demonstrated in Figure 2, the different mutations greatly impact the chances of survival. By thoroughly examining the aberrations present the prognosis will be that much more accurate. The course of the disease, or the prognosis, is unique for everyone..

By utilizing the various mutations to calculate a more accurate prognosis, researchers or clinicians can assist the patient in understanding their disease. This allows patients to mentally and physically prepare themselves for what's to come and comprehend the future of their disease. Treatment is even more vital. Patients with different mutations are going to need specific treatment options. The same thing will only work for some despite them all being part of a very small subcategory of a specific disease. Utilizing custom treatment methods would increase percentages across the board in things such as the OS and EFS rates. It would lead to healthier MRD counts and cure people faster and easier than before.

Discussion

Hyperdiploidy/Hypodiploidy:

One type of variation starts in the chromosomes. It occurs when there is an irregular chromosome count: hyperdiploid and hypodiploidy, an abnormally large number of chromosomes and an abnormally small number of chromosomes respectively. Cell division errors are the root cause of aneuploidies.[8] The chromosomal count is determined at birth and during gestation.[9] Studies examined have concluded that hyperdiploidy and hypodiploidy further build up leukemia development. Hypodiploid ALL (anywhere from 24-39 chromosomes) is associated with approximately 2% of ALL in children under the age of 12. High Hyperdiploid (51-67 chromosomes) is found in 25-30% of children with ALL and is extremely recurrent in ages 3-5. More genetic variations exist in specific genes.[10]

Hyperdiploidy and Hypodiploidy both can majorly change the prognosis of ALL. The prognosis of this abnormality also varies depending on the age group. For the "AYA" group, which symbolizes the adolescent and young adult group, in cases of B-ALL, patients who had an abnormally low count of chromosomes or hypodiploidy, less than 44 chromosomes, were said to have high risk. On the exact opposite degree, patients who had an abnormally high count of chromosomes or hyperdiploidy were said to have a much smaller risk.[11] Similar results were obtained when reviewing adult patients. It was noted that both aneuploidies had been connected to and resulted in lower overall survival rates (OFS) and chances of disease-free survival (DFS). Specifically, hypodiploidy was worse again. Lower hypodiploidy levels, 30-39 chromosomes, had massively lessened event-free survival (EFS) five years after. The EFS rates were around 13%-24%, symbolizing that 76-87% of patients either didn't survive the next five years or got majorly sick afterward. The overall survival rates (OS) were lower, at 13-28%. Higher levels of hyperdiploid, from 60-78 chromosomes, had

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some better results, with the five-year EFS at 49-50% and the OS rates at 53-58%.[12]

Hyperdiploidy and Hypodiploidy currently don't have any specific treatment plans. As of right now, these variations do not impact how medical professionals cure the disease. On the other hand, for most cases on this list, PH+ or PH- ALL will make a difference in how the patient reacts to different treatment methods. PH is the Philadelphia Chromosome. When this chromosome is found to be positive (+), it's said to be much more aggressive and is treated with Tyrosine Kinase Inhibitors (TKI) and corticosteroids along with chemotherapy. PH- ALL is standard ALL treatment. TKIs are a type of therapy that is specifically aimed at cancers. They are broken down into growth factors and tyrosine kinases, which are chemicals that control cell growth, and enzymes that control cell division.[13] Corticosteroids are steroids which are drugs that have similar effects to cortisol, which is a bodily hormone.[14]

ETV6:

ETV6 (ETS variant 6), is a transcription factor within the body which is required for survival and has a very important role in regulating cell's growth and development.[15] It is fundamental in finding Bone Marrow (BM) in mice. In 2015, the ETV6 gene was studied in a lab and tested on various mice. This is important because mice and humans share almost the same set of genes.[16] The results came out displaying that ETV6 is a gene which has various variations that can predispose people into developing ALL.[17] Studies which were published afterwards came out with the result that variations in ETV6 are recognized within approximately 1% of ALL patients below the age of 21.[18]

ETV6 mutations have had various effects on the prognosis of ALL. Various studies have been conducted involving patients with and without this gene examining different ethnicities with this variation. One study demonstrated the genetic variation coming as positive and representing an 80-97% EFS rate which is dramatically better than other subtypes. What arose uncertainty was a separate study demonstrating the same fusion demonstrating higher incidence, around 20-24% EFS.[19] This led to doubt whether this specific genetic alteration had much prognostic effect. This led to a new study involving two thousand, five hundred and thirty patients. They were divided on whether they had the mutation or not. The results ended up demonstrating that ETV6 mutations had a definite higher EFS and OS in pediatric patients. They showed that children who were positive for the ETV6 mutation ended up having positive responses early in treatment and had a much smaller count of risk factors during the initial first diagnosis.[20] With respect to mutation specific treatments, TKIs can be used for patients with the ETV6 mutations - including the ETV6-RUNX1 fusion with t(1;19)(q23;p13) which is usually mentioned separately.[21] The treatment for this mutation is discussed further below.

IKZF1:

IKZF1 encodes a protein known as IKAROS. IKAROS is a transcription factor known for containing six zinc fingers. These fingers allow and assist it to connect with DNA and collaborate with alternative proteins. It's extensively expressed within the hematopoietic system in which it does its job. The problem is that somatic mutations affect this gene which has also been repeatedly discovered within cases of B-ALL with especially higher risk levels. It stands out in cases expressing the oncoprotein BCR-ABL. Depending on their subtypes, these mutations have varied frequencies for patients with ALL.[22] In pediatric Philadelphia Chromosome (Ph) negative B-ALL, deletions are reported in approximately 15% of the cases. This number skyrockets and doubles to 30% in high-risk pediatric populations. The number of patients with this deletion increases in adult B-ALL, where the frequency of IKZF1 deletions reaches 30-50%. The highest percentage number is found in Ph Positive ALL.[23]

The IKZF1 gene has many aberrations and mutations possible within ALL, which have impacts. This gene has always been associated with being a poor prognostic marker within ALL or having a high likelihood of disease progression or recurrence and higher chances of death.[24] Deletions in the IKZF1 gene have commonly occurred in older patients. It's connected to higher minimal residual disease (MRD) levels, subsequent induction and consolidation, and higher white blood cell counts (WBC).[25] Because of these, the IKZF1 deletions are represented abnormally high in high-risk patients. After an extremely in-depth review and meta-analysis, it shows that IKZF1 deletions and mutations are associated with a higher likelihood of death and the disease getting worse.[26]

When observing the IKZF1 aberrations, it is noticed that these cells are in fact resistant to certain treatments and are harder to cure. Many therapeutic methods which are very commonly used in the treatment of ALL, especially B-ALL, don't work, including Dexamethasone, Vincristine, Asparaginase, Daunorubicin. Many studies have been placed and patients have been examined to arrive at the conclusion that there are successful therapeutic methods. These methods include, but aren't limited to Retinoids, FAK inhibitions, Retinoid receptor agonists.[27]

t(t;19)(q23;p13)/ETV6-RUNX1:

The gene t(1;19)(q23;p13) has a recurrent mutation in which it's translocated with the ETV6-RUNX1(TEL-AML1) fusion.[28] This alteration is believed to originate in the embryo, demonstrated by its being found within the blood from the umbilical cord. The fusion originates from a single cell, but in identical twins, it's commonly found in both, suggesting that the fusion originates in the embryo.[29] This fusion is considered to be the alteration most recurrent for patients under the age of 21 with B-ALL, happening in 20-25% of cases. This alteration isn't just found within patients; it's said to initiate leukemia.[30] The long delay between a patient with ETV6-RUNX1's birth to when they actually develop leukemia suggests that ETV6-RUNX1 isn't enough on its own to initiate leukemia. It hints that more genetic events such as the loss of the copy of the ETV6 gene, which didn't go through genetic rearrangement of any sort, loss of the PAX5, or a mutation for WHSC1.[31]

The ETV6-RUNX1 fusion with the three genes has been most commonly found in B-ALL compared to T-ALL, similar to many already-mentioned mutations. A study, or "multiplatform analysis," has been conducted with 304 patients with

B-ALL but focusing more on the ETV6-RUNX1 fusion instead of the t(t;19)(q23;p13) gene and came out to demonstrate that there was a very positive prognosis with high survival rates.[32] Opposing this, a separate study was completed on patients receiving intensive induction chemotherapy and found that the t(t;19) translocation was a well-described mutation associated with a poorer prognosis. This was very controversial with the new modern chemotherapy regimens and their impacts. This led to the conclusion that more studies had to be conducted to decide on this specific mutation fully.[33]

As mentioned in the subsection regarding ETV6, the ETV6-RUNX1 fusion with t(1;19)(q23;p13) can also be treated using TKIs. Many healthcare researchers have also attempted to change or interrupt the fusion proteins. A genetic screening method known as CRISPR-CAS9 has been used to detect or find these proteins. A method of solving these fusions is by disrupting other proteins using EWS-FLI1.[34]

MEF2D:

MEF2D or myocyte enhancer factor 2D is a necessary gene which has various jobs such as regulating differentiation and reprogramming which specific genes are expressed in the heart of persons above the age of 18.[35] Rearrangements in this gene are variations which studies have shown to be present in approximately 4% of childhood B-ALL cases and around 10% of adult B-ALL cases.[36] This genetic subtype demonstrates a specific immunophenotype which has minimal to no expression of the gene CD10 but comes positive for CD38 and cytoplasmicμ and definite expression profile.[37] These changes and rearrangements end up enhancing or increasing the strength of MEF2D's transcriptional activity, boosting HDAC9 expression and its awareness to histone deacetylase inhibitors.[38]

MEF2D mutations have quite a relationship with B-ALL. A similar study involving more than 300 patients involved different mutations and resulted in valuable information. The conclusion came out stating that all patients who have the MEF2D fusions form a unique group with pre-B cell immunophenotype and, unfortunately, is associated with poor prognosis and a poor clinical outcome. The five-year survival rates are 33.3% for children and 15.6% for adults. This specific mutation is commonly noted to require further studies for the molecular mechanisms underlying the oncogenic behavior of the gene.[39]

The MEF2D mutation has no current information about specific custom treatment. For this aberration standard treatment would be sufficient.[40]

IAMP21:

iAMP21, or chromosome 21 is a type or irregularity which doesn't involve chromosome count...but does focus on a specific chromosome. This chromosome has a variation in which it goes through intrachromosomal amplification. This variation is present in approximately 1% of all ALL for children. The most common age at diagnosis in which this variation is found is age nine. This variation is associated with an abnormally under-par blood cell count. The germline Robertsonian translocation rob (15;21) and a germline ring chromosome 21 are both germline variations in the genes which are said to increase the chances of iAMP21 mutations.[41]

The chromosomal abnormality known as and referred to as iAMP21 has very serious and noticeable effects in ALL. In 2003, this abnormality was announced to be its own specific cytogenetic subgroup of BCB-ALL.42 Some characteristics stay similar in patients with this aberration such as the feature of having the highest-level amplification spanning 5.1 Mb of chromosome 21 from 32.8 to 37.9 Mb. Overall studies have demonstrated some poor outcomes for this unique difference. It was found that patients who had iAMP21 would have an extremely worsened five-year EFS rate in contrast to patients on BCP-ALL without iAMP21. The OS rates were 71% which was still worse in comparison to other patients. iAMP21 is defined as a very high-risk disease with poor prognosis today.[43]

Generally, in case studies of ALL patients with iAMP21 are observed to respond poorly to standard treatment. While the treatment processes don't appear to physically harm the patient and the disease may leave their body, the risk of the disease returning or relapsing is high. The most recent articles and cases have demonstrated that by utilizing intensified therapy methods and high-risk arms, the chances of the disease returning decrease

DUX4 Translocation:

Translocation of the DUX4 gene to the immunoglobulin heavy chain locus (IGH). This translocation is a genetic mutation that is characterized by ending up overexpressing for the 3' shortened DUX4 protein. This protein can be found on chromosome 4q/10q. It encodes a transcription fact which then initiates the gene expression for many genes within still-developing embryos.[44] The DUX4 ends up being silenced in most somatic cells. This mutation or subtype happens within around 5-10% of every single B-ALL case in all ages.[45]

Studies have demonstrated that the IGH-DUX4 translocation has had various effects on determining the prognosis of given patients. This mutation is said to be a very powerful mutation that can have dire consequences but is also, in fact, extremely rare. This mutation seemingly has positives and negatives, such as having an extremely positive overall outcome rate with the five-year cumulative risk of relapse [CIR} being only 8.9%.[46] An average of 97.8% OS rate indicates that patients with this specific mutation are more likely to live through the disease. In contrast to this, there are very unhealthy and poor MRD rates, which were counted on day 33 during the examined case study.[47]

Similar to the MEF2D aberration, standard treatment would be sufficient for this mutation.

■ Conclusion

ALL is a disease impacted by a myriad of genetic mutations that affect disease progression in diverse ways. As shown, the various mutations do affect the overall survival rates, and by understanding each variation doctors can better inform patients. This paper examined the impact of many of these aberrations as well as identifying corresponding treatment methods. Such targeted therapeutics can improve patient prognosis and their existence underscores the importance of genetic testing. There is still a lot of research to be done regarding genetic variants within this disease.

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A specific instance of an area which requires further research is the conflicting information around individual variants. For example, there are many studies published which provide mixed information regarding the ETV6-RUNX1 fusion with the t(1;19)(q23;p13) gene. This paper identified their contrasting results, but future studies could consider exploring the causes for these differences. More studies in this field could save countless lives of patients with this mutation. This paper argues that prognosis and treatment are both directable by utilizing and examining the different genetic variations patient by patient. Especially in iAMP21 and PH+ ALL; in which both respond poorly to standard treatment, this paper demonstrated that it is vital to examine the mutations to assess which treatment methods should be used or developed.

By developing a larger focus and research effort on examining genetic mutations within all diseases, scientists and clinicians can improve their ability to predict the chances of any patient to develop many diseases. As this predictive power improves, people can get tested for aberrations very early in life and continue this testing for decades. This would provide patients with an idea of what diseases they are at high risk for and what they can do to lower those risks. As more people take blood tests on a consistent basis, companies will be able to manufacture more at a lower cost. This, in turn, will increase the number of people with access to the test and this provides more data for scientists to study. The study of genetic variants or mutations has a much larger impact than many realize, whether it's improving treatment and prognosis or preventing the disease from entering the body at all.

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