Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Diyala
College of Medicine

Leukaemia and Down syndrome

Written By:

Zahraa Naser

2022

Supervised By:

Dr. Zahraa Najah

بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)

[المجادلة: ١١]

Contents :

Acknowledgement

First, I would like to express my sincere gratitude to my supervisor, Dr. Zahraa Najah, for her enthusiasm, patience, insightful comments, and helpful information that have helped me tremendously at all times in my project.

I would like also to express my sincere thanks to the faculty of college of medicine at University of Diyala for what they taught me and their encouragement and support.

Last but not least, deepest thanks and appreciation to my beloved parent who are the source of my strength and the reason why I'm here today, who continually provide their moral, spiritual, emotional and financial support. My special thanks to my beloved sisters for their unconditional and endless love and support, Finally, I Dedicate To The Soul Of My Uncle, One Of Those With This Syndrome.

Abstract

Children with Down syndrome (DS) have a significantly increased risk of childhood leukemia, in particular acute megakaryoblastic leukemia (AMKL) and acute lymphoblastic leukemia (DS-ALL). A pre-leukemia, called transient myeloproliferative disorder (TMD), characterised by a GATA binding protein 1 (*GATA1*) mutation, affects up to 30% of newborns with DS. In most cases, the pre-leukemia regresses spontaneously, however one-quarter of these children will go on to develop AMKL or myelodysplastic syndrome (MDS) .

Although this is a serious disease, with current medical knowledge and treatment long-term outcomes have significantly improved over the last 20 years. Testing at birth can identify babies with Down's syndrome who are at increased risk so that they can have appropriate follow-up and earlier treatment.So this review aims to identify potential impacts of new research on how we manage children with DS, pre-leukemia and leukemia.

Introduction

Leukemia is a malignant condition involving the excess production of immature or abnormal leukocytes, which eventually suppresses the production of normal blood cells and results in symptoms related to cytopenias.Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for self-renewal. Abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells [(1)] .

Classification of Leukemia :

- Acute myeloid leukemia (AML): 33%
- Acute lymphoblastic leukemia (ALL): 10%
- Chronic myeloid leukemia (CML): 14%
- Chronic lymphocytic leukemia (CLL): 35%
- Other leukemias: 8%

There is a type of leukaemia called Congenital or Transient leukemia , commonly occur in Down syndrome.Trisomy 21 is the most common chromosomal disorder in humans and is the genetic basis of Down syndrome This multisystem disorder results in numerous pheno- typic features, including craniofacial abnormalities and cognitive impairment Although solid tumours are less frequent in the DS than the non-DS population [3–5],

The risk of developing acute megakaryoblastic leukemia (AMKL), which was a relatively rare subtype of acute myeloid leukemia (AML), was increased 500-fold in children with DS as compared to the general non-DS population; and risk of acute lymphoblastic leukemia (ALL) was 20-fold greater in children with DS [(1)] .

Typically in childhood, ALL was significantly more common than AML. However in DS, the ratio of ALL to AML was 1.7 for children under 15 years of age. For the general population of non-DS children, the equivalent ratio was 6.5 [(1)] .

In this review, we will focus on recent studies that have improved our understanding of leukemogenesis in DS, particularly myeloid leukemia of Down syndrome (ML-DS).

In individuals with DS have a higher risk of developing haematopoietic disorders. DS children are at greater risk of developing acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML), by an estimated factor of 27-fold and 150-fold compared with the general population.

Review of Literature:

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system.Many types of leukemia exist. Some forms of leukemia are more common in children. Other forms of leukemia occur mostly in adults.Leukemia usually involves the white blood cells. Your white blood cells are potent infection fighters — they normally grow and divide in an orderly way, as your body needs them. But in people with leukemia, the bone marrow produces an excessive amount of abnormal white blood cells, which don't function properly .In general, leukemia is thought to occur when some blood cells acquire changes (mutations) in their genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In leukemia, the mutations tell the blood cells to continue growing and dividing.When this happens, blood cell production becomes out of control. Over time, these abnormal cells can crowd out healthy blood cells in the bone marrow, leading to fewer healthy white blood cells, red blood cells and platelets, causing the signs and symptoms of leukemia[(2)] .

Risk factors that may increase your risk of developing some types of leukemia include:

1. **Previous cancer treatment.** People who've had certain types of chemotherapy and radiation therapy for other cancers have an increased risk of developing certain types of leukemia.
2. **Exposure to certain chemicals.** Exposure to certain chemicals, such as benzene — which is found in gasoline and is used by the chemical industry — is linked to an increased risk of some kinds of leukemia.
3. **Smoking.** Smoking cigarettes increases the risk of acute myelogenous leukemia.
4. **Family history of leukemia.** If members of your family have been diagnosed with leukemia, your risk of the disease may be increased.
5. **Genetic disorders.** Genetic abnormalities seem to play a role in the development of leukemia. Certain genetic disorders, such as Down syndrome, are associated with an increased risk of leukemia is **10 to 15 times more common in children with Down syndrome**. In particular, acute lymphoblastic leukemia is 20 times more common and the megakaryoblastic form of acute myeloid leukemia (acute megakaryoblastic leukemia), is 500 times more common[(2)] .

Leukaemia and Down syndrome

Transient leukaemia in neonates with Down syndrome usually 5-10% of them will be affected ,known as a transient abnormal myloposis TAM or A transient myloproleferative disorder TMD. Developed during fetal life presented in first weeks of life and presented with leukocytosis and circulating blast. most cases spontaneously resolve With (2_3) months without treatment. in sever cases (10_20%) may develop progressive disease within days or weeks due to infiltration of blast cells to the liver in associated with liver fibrosis may presented with pleural pericardial effusion, ascites , hepatomegaly, liver dysfunction, coagulopathy are common and in this condition treatment with low dose of cytosine arabinoside is effective [3] .

Is usually caused by acquired mutation in GATA in fetal liver hematopic cells present in 30% of all Down syndrome neonate but only half of them may presented with TAM.Other cases are silent because the mutation clone are very small. 10% of cases with silent GATA1 or TAM may develop Acute megakaryoblastic leukemia (AMKL) before 5 years usually between (12_ 18 months) . mutation in cohesin complex gene, it is most important cause of transformation TAM to AMKL.AMKL unlike TAM isn't transient must be treated with chemotherapy associated with good outcome about (80_90%) long term survival rate [3] .

Aetiology Of Leukemia in Down syndrome

Trisomy 21 foetal livers have an abnormal haematopoietic development. Specifically, there is an increased frequency of haematopoietic stem cells (HSCs) which also show increased clonogenicity and megakaryocytic–erythroid output. This results in an expansion of megakaryocyte erythroid progenitors and a decrease in granulocyte macrophage progenitors .In addition, B-cell differentiation is impaired .The mechanisms by which the extra copy of chromosome 21 alters normal blood production remain unclear [6] .

Several genes with important functions in haematopoietic development, including ERG, ETS2 and RUNX1, are located on chromosome 21. Overexpression of Erg and Ets2 induce megakaryocytic expansion and contribute to a myeloproliferative phenotype in mice [7] [9]. In addition, overexpression of another chromosome 21 gene, Dyrk1a, induces a marked megakaryocytic expansion However, the role of the increased dosage of chromosome 21 genes on altered trisomic foetal liver haematopoiesis is unclear. On one hand, foetal liver(HSCs)only show extremely modest increases in expression of ERG and RUNX1 .On the other, targeted deletion of RUNX1, ETS2 and ERG in human trisomy 21-induced pluripotent stem cells (iPSCs) suppresses the altered differentiation phenotypes .

Trisomy 21 can also interfere with gene expression by altering DNA methylation patterns. DNA methylation profiling at different stages of ML-DS development revealed hypomethylation in early stages and

hypermethylation in advanced stages .Interestingly, loss of methylation was found to affect genes associated with developmental disorders, while gain of methylation was observed in key genes involved in haematopoiesis. Similarly, haematopoietic cells of DS newborns have differential methylation patterns at promoter/enhancer regions relative to non-DS newborns .Specifically, the promoter regions of two genes involved in megakaryopoiesis (RUNX1 and FLI1) were found to be hypermethylated in DS samples [8] .

All TMD and ML-DS cases carry somatic mutations in GATA1 resulting in the introducation of a premature stop codon which promotes the exclusive translation of GATA1s. Mechanistically, the long and short GATA1 isoforms have similar but non-identical binding patterns on the genome ,specific genes and enhancers are differently bound by the two isoforms, which could explain the skewed differentiation profile of GATA1s-expressing cells. The short isoform is less efficient at activating erythroid gene pathways in MEPs than the full-length GATA1 .Moreover, analysis of chromatin occupancy and gene expression during erythropoiesis of GATA1s mice shows that normal murine foetal haematopoiesis is impaired as a result of deregulation in gene pathways of erythroid and megakaryocytic lineages. Interestingly, while GATA1s binding is reduced at erythroid genes, its activity is enhanced at important megakaryocytic genes [10] .

Spectrum of Mutations Driving the Transition from TMD to ML-DS :

The progression from TMD to ML-DS requires at least one additional mutation in the GATA1s clones. The advent of large-scale sequencing studies over the last decade has enabled the identification of recurrent mutations in ML-DS patients [(11) (12)].The most frequent alterations can be grouped into two major categories genes encoding for transcriptional regulators and genes encoding for signalling pathway mediators. Strikingly, among the first group .The most frequently mutated genes belong to the cohesin complex. Between 38% and 53% of patients have mutations in cohesin, compared to only 11% of non-DS AMKL patients .This may indicate that the selective advantage of cohesin mutations in ML-DS could be related to trisomy 21-specific features. CTCF,which cooperates with cohesin in the formation of topologically associating domains (TADs), is also extremely frequently mutated (11–20% of cases). In contrast to cohesin, CTCF is also recurrently mutated in non-DS AMKL (10–21%) [(11)].In addition, mutations in epigenetic regulators are also frequent, such as in the polycomb repressive complex 2 (PRC2) components EZH2 and SUZ12 or the chromatin modifier KANSL1. Analysis of the clonal origin of mutations shows that cohesin, CTCF and EZH2 mutations may have essential roles in the early stages of ML-DS progression .Deletions, missense, nonsense and frameshift mutations, usually leading to a loss of function, are found in transcription factors including RUNX1, TP53, WT1, CREBBP and MYC (~8%)..[(13)] .

Acquired mutations in GATA1 in themegakaryoblastic leukemia of Down syndrome(5) :

Children with Down syndrome have a 10–20-fold elevated risk of developing leukemia, particularly acute megakaryoblastic leukemia (AMKL) While a subset of pediatric AMKLs is associated with the translocation and expression of a mutant fusion protein 2, 3, the genetic alterations that promote [13] .

Down syndrome–related AMKL (DS-AMKL) have remained elusive. Here we show that leukemic cells from every individual with DS-AMKL that we examined contain mutations in GATA1, encoding the essential hematopoietic transcription factor GATA1 (GATA binding protein 1 or globin transcription factor 1). Each mutation results in the introduction of a premature stop codon in the gene sequence that encodes the amino-terminal activation domain. These mutations prevent synthesis of full-length GATA1, but not synthesis of a shorter variant that is initiated downstream. We show that the shorter GATA1 protein, which lacks the N-terminal activation domain, binds DNA and interacts with its essential cofactor Friend of GATA1 (FOG1; encoded by ZFPM1) 4 to the same extent as does full-length GATA1, but has a reduced transactivation potential. Although some reports suggest that the activation domain is dispensable in cell-culture models of hematopoiesis ،one study has shown that it is

required for normal development in vivo 7. Together, these findings indicate that loss of wildtype GATA1 constitutes one step in the pathogenesis of AMKL in Down syndrome [13] [14] .

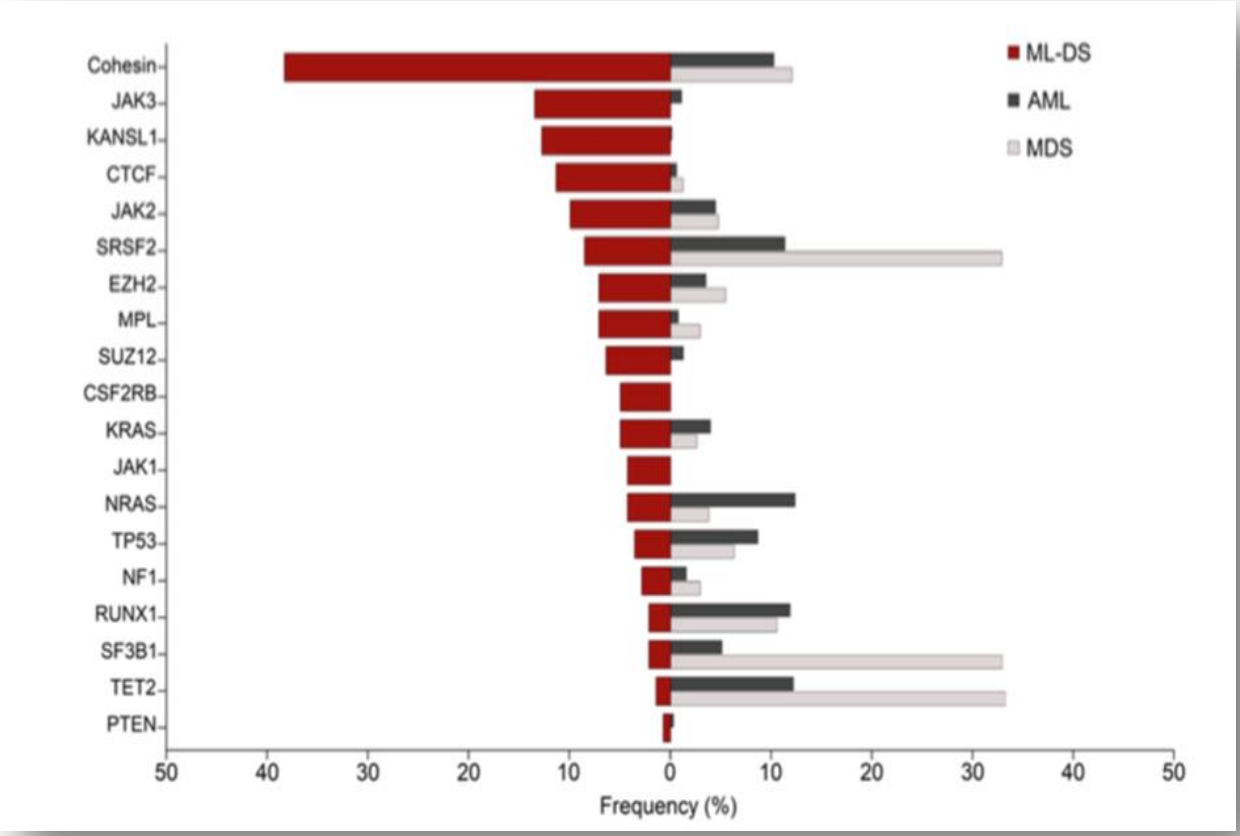

Figure 1: Comparative frequencies of commonly mutated genes in ML-DS, AML and MDS.

Prevalence of leukaemia in Down's syndrome

It found that 2.8% of children with Down syndrome were diagnosed with leukemia, compared to 0.05% of other children. Compared to other children, kids with Down syndrome had a higher risk of AML before age 5 and a higher risk of acute lymphoid leukemia (ALL) [17] .

Children with Down's syndrome are at an increased risk of developing any type of acute leukaemia. In particular, they are 150 times more likely to develop acute myeloid leukaemia (AML) and are at a 33 times greater risk of developing acute lymphoblastic leukaemia (ALL).

Around 10% of all newborns with Down's syndrome are born with a unique "pre-leukaemia" condition known as transient leukaemia (TL). In most cases, TL will not result in symptoms and it will resolve spontaneously without any treatment. However, 1 out of 5 patients with TL will go on to develop AML, also known as myeloid leukaemia of Down's syndrome[17].This is a data review for the incidence and prevalence of Leukemia in child with Down syndrome in many study , research made in last 20 years ago such as the result of study made in Israel in 2001 marked,statistically significant excess of Leukemia in Down syndrome subjects; A 25-fold excess morbidity for DS subjects born between 1979 and 1995 and a 7-fold excess morbidity for DS subjects born before 1979, mostly noted for the age groups of 0–19 and 20–39 years. [15] [16].

Result of study made in New York State,2018, Statistically significant of Leukemia in Down syndrome subject :Birth defect status was significantly associated with age at ALL

diagnosis. , 11.0% had DS, 6.0% had other birth defects, and 83.0% had no birth defects. Children with DS were more likely to be diagnosed with AML at a younger age and showed the best survival [18] .

Result of study of Leukemia Risk in a Cohort of 3.9 Million Children with and without Down Syndrome 2021,Leukaemia was diagnosed in 124 of 4401 children with DS and 1941 of 3 900 998 other children. In children with DS, the cumulative incidence of (AML) was 1405/100 000 (95% CI 1076-1806) at age 4 years and unchanged at age 14 years. The cumulative incidence of (ALL)in children with DS was 1059/100 000 (95% CI 755-1451) at age 4 and 1714/100 000 (95% CI 1264-2276) at age 14 years. Children with Down syndrome had a greater risk of AML before age 5 years than other children [19] .

Result of leukemia in American society 2009, statistically significant of leukemia in Down syndrome subject:Patients with DS are also at a markedly increased risk for childhood ALL. Indeed, DS-ALL is more frequent than DS-AMKL.5 In most published multi-institutional ALL protocols, DS-ALL comprises approximately 1% to 3% of total patients(20)(21) . Result of study of cancer among persons with Down syndrome 2010,

The incidence of cancer in children and adults with (DS) appears the same as in the general population. The distribution of tumor types, was markedly different. The risk for leukemia in children with DS is 10–20-fold higher than in children without DS. In contrast, solid tumors both of childhood and adult age are markedly less frequent in people with DS [20].

Leukemia symptoms in children with Down syndrome :

- more frequent infections.
- easy bleeding and bruising.
- bleeding gums or nosebleeds.
- pale skin.
- cold sensitivity.
- fatigue and weakness.
- fever.
- breathing difficulties, such as chronic cough or shortness of breath [4] .

Treatment and outcome for ML-DS

Children treated for ML-DS have a significantly higher disease-free survival (DFS) compared to other children treated for AML (DFS 88-89% compared to 42%, P<0.001) .Arguably this could be due to AML subtype but DS-AMKL also requires less intense therapy to achieve cure as compared to non-DS AMKL, indicating that children with ML-DS are more responsive to chemotherapy . A possible explanation for the chemosensitivity of ML-DS is an alteration in cytarabine drug metabolism due to reduced cytidine deaminase gene expression in ML-DS or increased expression of cystathionine β-synthase, which is encoded by

chromosome 21 .Cytarabine is a key drug in successful therapy against ML-DS and AML [4] .

Children with DS who develop AMKL beyond the age of 4 years old are thought to represent a different cohort of patients. Age >4 years old is a poor prognosticator, conferring a 5-year EFS of 33%, compared to 81% for DS children with myeloid leukemia aged <4 years old .Children who are older than 4 years of age, without *GATA1* mutations, are more likely to have similar cytogenetic aberrations to sporadic (non-DS) AML .These children are more likely to require more intensive therapy, as compared to children with ML-DS .In addition, DS patients with TMD have also been described who progress to ALL, although this is very rare and occurs much less often than ML-DS [4] .

Conclusions

A major re-appraisal in attitudes towards DS is required to ensure that the medical and social needs of people with the disorder are adequately met across their entire lifespan. In particular, specific recognition of the comorbidities that can arise at different ages is needed, accompanied by the provision of appropriate levels of care and management.

Many Population-based studies that will document the incidence of TMD and its evolution to AML are in progress. Differential display by microarray technologies may reveal what genes are turned off and on during regression of TMD and subsequent development of AML. So far, molecular studies have not yielded a unifying

explanation for the predisposition for leukaemia in DS children.

Nonetheless, the continued investigation of DS and leukaemia will undoubtedly provide answers to our questions about aetiology and pathogenesis of leukaemia in all children.

Therefore, the ultimate aim is to provide early diagnosis of all types of leukaemia or pre leukaemia and to identify novel therapeutic targets that may improve outcome for all children with DS, pre-leukemia and leukemia.

References

1. Hitzler JK, Zipursky A. Origins of leukaemia in children with Down syndrome. Nat Rev Cancer 2005;5:11-20. [PubMed] [Google Scholar]

2. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355:165-9. [PubMed] [Google Scholar]

3. A Victor Hoffbrand , Dniel Catovsky ,Edward GD Tuddenham and Anthrony R:Postgraduate Haematology , Sixth edition,2011. chapter 22 .p397

4. Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. Blood 2009;113:2619-28. [PMC free article]
[PubMed] [Google Scholar]

5_Roy A, Roberts I, Norton A, et al. Acute megakaryoblastic leukaemia (AMKL) and transient myeloproliferative disorder (TMD) in Down syndrome: a multi-step model of myeloid leukaemogenesis. Br J Haematol 2009;147:3-12. [PubMed] [Google Scholar]

6_Wagenblast, E.; Araújo, J.; Gan, O.I.; Cutting, S.K.; Murison, A.; Krivdova, G.; Azkanaz, M.; McLeod, J.L.; Smith, S.A.; Gratton, B.A.; et al. Mapping the cellular origin and early evolution of leukemia in Down syndrome. Science 2021, 373. [CrossRef] [PubMed]

7_Stankiewicz, M.J.; Crispino, J.D. ETS2 and ERG promote megakaryopoiesis and synergize with alterations in GATA-1 to immortalize hematopoietic progenitor cells. Blood 2009, 113, 3337–3347. [CrossRef] [PubMed]

8_Ng, A.P.; Hyland, C.D.; Metcalf, D.; Carmichael, C.L.; Loughran, S.J.; Di Rago, L.; Kile, B.T.; Alexander, W.S. Trisomy of Erg is required for myeloproliferation in a mouse model of Down syndrome. Blood 2010, 115, 3966–3969. [CrossRef] [PubMed]

9. Rainis, L.; Toki, T.; Pimanda, J.E.; Rosenthal, E.; Machol, K.; Strehl, S.; Göttgens, B.; Ito, E.; Izraeli, S. The proto-oncogene ERG in megakaryoblastic leukemias. Cancer Res. 2005, 65, 7596–7602. [CrossRef] [PubMed]

10_Malinge, S.; Bliss-Moreau, M.; Kirsammer, G.; Diebold, L.; Chlon, T.; Gurbuxani, S.; Crispino, J.D. Increased dosage of the chromosome 21 ortholog Dyrk1a promotes megakaryoblastic leukemia in a murine model of down syndrome. J. Clin. Investig. 2012, 122, 948–962. [CrossRef]

11_Yoshida, K.; Toki, T.; Okuno, Y.; Kanezaki, R.; Shiraishi, Y.; Sato-Otsubo, A.; Sanada, M.; Park, M.J.; Terui, K.; Suzuki, H.; et al. The
landscape of somatic mutations in Down syndrome-related myeloid disorders. Nat. Genet. 2013, 45, 1293–1301. [CrossRef]

12_ Nikolaev, S.I.; Santoni, F.; Vannier, A.; Falconnet, E.; Giarin, E.; Basso, G.; Hoischen, A.; Veltman, J.A.; Groet, J.; Nizetic, D.; et al. Exome sequencing identifies putative drivers of progression of transient myeloproliferative disorder to AMKL in infants with Down syndrome. Blood 2013, 122, 554–561. [CrossRef] [PubMed]

13_Labuhn, M.; Perkins, K.; Matzk, S.; Varghese, L.; Garnett, C.; Papaemmanuil, E.; Metzner, M.; Kennedy, A.; Amstislavskiy, V.; Risch, T.; et al. Mechanisms of Progression of Myeloid Preleukemia to Transformed Myeloid Leukemia in Children with Down Syndrome. Cancer Cell 2019, 36, 123–138.e10. [CrossRef]

14_ Cancer Genome Atlas Research Network. Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia. N. Engl. J. Med. 2013, 368, 2059–2074. [CrossRef] [PubMed]

15_ Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355: 165–9.
CrossrefCASPubMedWeb of Science®Google Scholar

16_Rothman KJ, Boice JD, Jr. Epidemiologic analysis with programmable calculator. Washington, DC: USA 6PO DHEW publications (NIH), 1979: 79–1649.
Google Scholar

17_Department of Epidemiology, UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095, United States.

18_Division of Pediatric Oncology, University of Minnesota Health Sciences Center, Minneapolis, Minn. USA

19_Epidemiology Strategy Group of the Childrens Cancer Study Group, Los Angeles, Calif. USA

20_Hasle H. Pattern of malignant disorders in individuals with Down's syndrome., Lancet Oncol, 2001, vol. 2 (pg. 429-436)

21_Pui CH, Raimondi SC, Borowitz MJ, et al. Immunophenotypes and karyotypes of leukemic cells in children with Down syndrome and acute lymphoblastic leukemia., J Clin Oncol, 1993, vol. 11 (pg. 1361-1367) Google ScholarCrossref .